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(54) Title: BICYCLIC BENZAMIDE COMPOUNDS AS HISTAMINE H3 RECEPTOR LIGAND USEFUL IN THE TREAT-
MENT OF NEUROLOGICAL DISEASES

(57) Abstract: The present invention relates to novel bicyclic benzamide derivatives having pharmacological activity, processes for
their preparation, to compositions containing them and to their use in the treatment of neurological and psychiatric disorders.

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BICYCLIC BENZAMIDE COMPOUNDS AS HISTAMINE H₃ RECEPTOR LIGAND USEFUL IN THE TREATMENT OF NEUROLOGICAL DISEASES

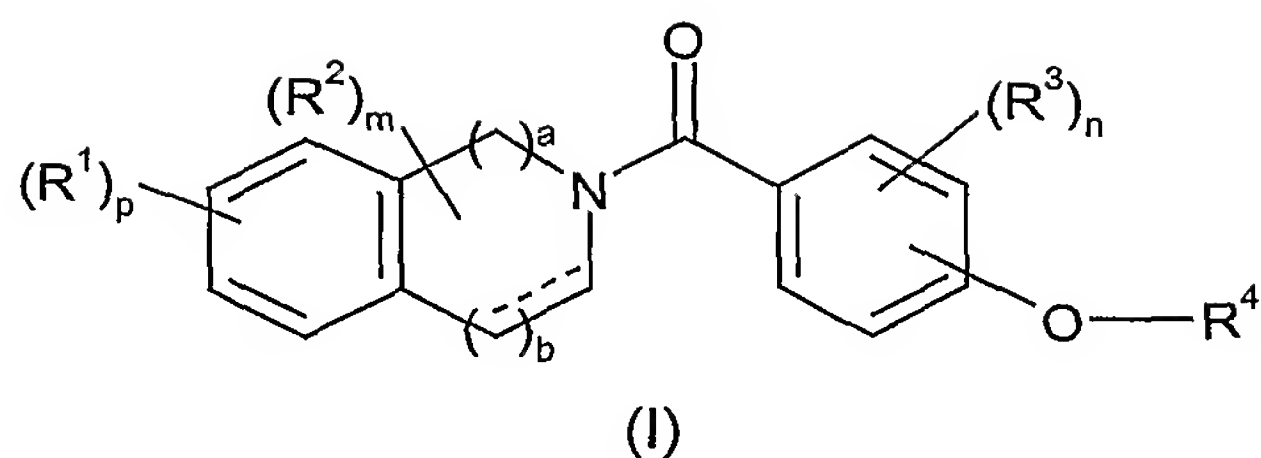
5 The present invention relates to novel bicyclic benzamide derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of neurological and psychiatric disorders.

10 WO 02/76925 (Eli Lilly), WO 00/06254 (Societe Civile Bioprojet), WO 01/66534 (Abbott Laboratories) and WO 02/12190 (Ortho McNeil Pharmaceutical Inc) describe a series of compounds which are claimed to be histamine H₃ antagonists. WO 02/094788 (Eli Lilly and Company) describe a series of substituted tetrahydroquinoline derivatives which are claimed to be useful in the treatment of diseases associated with aberrant physiological responses to endogenous estrogen. WO 01/23374 (SmithKline Beecham plc) describe a series of piperazine derivatives as 5-HT_{1B} antagonists which are claimed to be useful in the treatment of CNS disorders. WO 98/40385 (Novo Nordisk) describe a series of
15 tetrahydrothienopyridine derivatives which are claimed to be useful in diseases related to glucose metabolic pathways. WO 95/34540 and JP 09221476 (both Otsuka Pharm Co) describe a series of benzoheterocyclic derivatives as vasopressin or oxytocin modulators which are claimed to be useful in a variety of disorders. WO 01/66520 (Ono Pharm Co) describe a series of indole derivatives as prostaglandin D antagonists which are claimed
20 to be useful in allergic diseases, pruritus and cerebrovascular disease.

The histamine H₃ receptor is predominantly expressed in the mammalian central nervous system (CNS), with minimal expression in peripheral tissues except on some sympathetic nerves (Leurs *et al.*, (1998), Trends Pharmacol. Sci. **19**, 177-183).
25 Activation of H₃ receptors by selective agonists or histamine results in the inhibition of neurotransmitter release from a variety of different nerve populations, including histaminergic and cholinergic neurons (Schlicker *et al.*, (1994), Fundam. Clin. Pharmacol. **8**, 128-137). Additionally, *in vitro* and *in vivo* studies have shown that H₃ antagonists can facilitate neurotransmitter release in brain areas such as the cerebral
30 cortex and hippocampus, relevant to cognition (Onodera *et al.*, (1998), In: The Histamine H₃ receptor, ed Leurs and Timmerman, pp255-267, Elsevier Science B.V.). Moreover, a number of reports in the literature have demonstrated the cognitive enhancing properties of H₃ antagonists (e.g. thioperamide, clobenpropit, ciproxifan and GT-2331) in rodent models including the five choice task, object recognition, elevated plus maze,
35 acquisition of novel task and passive avoidance (Giovanni *et al.*, (1999), Behav. Brain Res. **104**, 147-155). These data suggest that novel H₃ antagonists and/or inverse agonists such as the current series could be useful for the treatment of cognitive impairments in neurological diseases such as Alzheimer's disease and related neurodegenerative disorders.

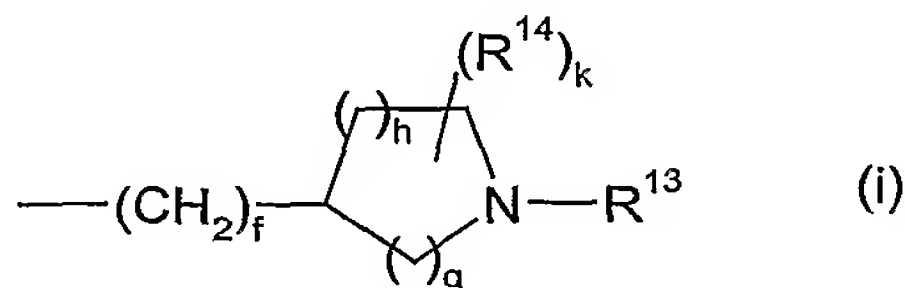
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The present invention provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



wherein:

- 5 R^1 and R^2 independently represent halogen, hydroxy, cyano, nitro, oxo, haloC₁₋₆ alkyl, polyhaloC₁₋₆ alkyl, haloC₁₋₆ alkoxy, polyhaloC₁₋₆ alkoxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, arylC₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkoxyC₁₋₆ alkyl, C₃₋₇ cycloalkylC₁₋₆ alkoxy, C₁₋₆ alkanoyl, C₁₋₆ alkoxy carbonyl, aryl, heteroaryl, heterocyclyl, arylC₁₋₆ alkyl, heteroarylC₁₋₆ alkyl, heterocyclylC₁₋₆ alkyl, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylsulfinyl, C₁₋₆ alkylsulfonyloxy, C₁₋₆ alkylsulfonylC₁₋₆ alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC₁₋₆ alkyl, aryloxy, -CO-aryl, -CO-heterocyclyl, -CO-heteroaryl, C₁₋₆ alkylsulfonamidoC₁₋₆ alkyl, C₁₋₆ alkylamidoC₁₋₆ alkyl, arylsulfonamido, arylaminosulfonyl, arylsulfonamidoC₁₋₆ alkyl, arylcarboxamidoC₁₋₆ alkyl, aroylC₁₋₆ alkyl, arylC₁₋₆ alkanoyl, or a group NR¹⁵R¹⁶, -NR¹⁵CO-aryl, -NR¹⁵CO-heterocyclyl, -NR¹⁵CO-heteroaryl, -CONR¹⁵R¹⁶, -NR¹⁵COR¹⁶, -NR¹⁵SO₂R¹⁶ or -
- 10 SO₂NR¹⁵R¹⁶, wherein R¹⁵ and R¹⁶ independently represent hydrogen or C₁₋₆ alkyl; wherein said aryl, heteroaryl and heterocyclyl groups of R¹ and R² may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different and which are selected from halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, oxo, CF₃, OCF₃, CN, C₁₋₆ alkanoyl, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylsulfonyloxy, C₁₋₆ alkylamido or C₁₋₆ alkylsulfonamido;
- 15 a and b independently represent 0, 1 or 2, such that a and b cannot both represent 0; ----- is a single or double bond;
- R³ represents halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, cyano, amino or trifluoromethyl;
- m and n independently represent 0, 1 or 2;
- 20 p represents an integer from 0 to 3, such that when p is an integer greater than 1, two R¹ groups may instead be linked to form a heterocyclyl group;
- R⁴ represents -(CH₂)_q-NR¹¹R¹² or a group of formula (i):




- 30 wherein q is 2, 3 or 4;
- R¹¹ and R¹² independently represent C₁₋₆ alkyl or together with the nitrogen atom to which they are attached represent an N-linked heterocyclic group optionally substituted by one or two R¹⁷ groups;
- 35 R¹³ represents hydrogen, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, -C₁₋₆ alkyl-aryl or heterocyclyl;

R¹⁴ and R¹⁷ independently represent halogen, C₁₋₆ alkyl, haloC₁₋₆ alkyl, OH, diC₁₋₆ alkylamino or C₁₋₆ alkoxy;

f and k independently represent 0, 1 or 2;

g is 0, 1 or 2 and h is 0, 1, 2 or 3, such that g and h cannot both be 0;


5 or solvates thereof.

In one particular aspect of the present invention, when a represents 0, b represents 2,  is a single bond and m represents 1, R² represents a group other than optionally substituted phenyl.

10

In another particular aspect of the present invention, when R⁴ represents a group of formula (i), f represents 0 and p represents 1, R¹ represents a group other than optionally substituted piperazinyl.

15

In another particular aspect of the present invention, when R⁴ represents 4-morpholinylethyl or pyrrolidinylmethyl, m represents 1 and  is a single bond, R² represents a group other than C₁₋₆ alkyl or optionally substituted aryl.

20

In another particular aspect of the present invention, when a represents 0, b represents 2 or 3 and R⁴ is a group other than pyrrolidinylalkyl.

25

In another particular aspect of the present invention, there is provided a compound of formula (I) as defined above wherein a represents 0, b represents 1 and p represents 1, R¹ is a group other than C₁₋₆ alkoxycarbonyl, C₁₋₆ alkylamidoC₁₋₆ alkyl or CONR¹⁵R¹⁶.

30

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine and the term 'polyhalo' is used herein to refer to a moiety containing more than one (eg. 2-5) of said halogen atoms.

The term "aryl" includes single and fused rings wherein at least one ring is aromatic, for example, phenyl, naphthyl and tetrahydronaphthalenyl.

35

The term "heterocyclyl" is intended to mean a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring containing 1 to 3 heteroatoms selected from oxygen or nitrogen. Suitable examples of such monocyclic rings include pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, 1,3-dioxolane, diazepanyl and azepanyl.

40

The term "heteroaryl" is intended to mean a 5-7 membered monocyclic aromatic or a fused 8-11 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings

include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl,
 5 naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

Preferably, m represents 0 or 1, more preferably 0.

10 Preferably, p represents 0, 1 or 2, more preferably 0 or 1, especially 0.

When present, R^1 is preferably halogen (eg. fluorine, bromine or chlorine), hydroxy, cyano, nitro, $-NR^{15}R^{16}$ (eg. NH_2), $-NR^{15}COR^{16}$ (eg. $-NH$ -acetyl), polyhalo C_{1-6} alkyl (eg. CF_3), heterocyclyl (eg. pyrrolidinyl optionally substituted by one or two oxo groups), C_{1-6} alkyl (eg. methyl), C_{1-6} alkoxy (eg. methoxy), C_{1-6} alkylsulfonyl (eg. $-SO_2Me$), C_{1-6} alkylsulfinyl (eg. $-SOMe$), C_{1-6} alkanoyl (eg. $-COMe$), arylsulfonamido (eg. $-NHSO_2Ph$),
 15 arylaminosulfonyl (eg. $-SO_2NHPh$), $-NR^{15}SO_2R^{16}$ (eg. $-NHSO_2Me$), $-SO_2NR^{15}R^{16}$ (eg. $SO_2N(Me_2)$) or $-CO$ -heterocyclyl (eg. $-CO$ -morpholinyl or $-CO$ -pyrrolidinyl).

In one preferred embodiment, p represents 2 and both R^1 groups are linked to form a heterocyclyl group (eg. 1,3-dioxolane).

20 When present, R^1 is more preferably halogen (eg. fluorine) or cyano, especially fluorine. When present, R^2 is preferably C_{1-6} alkyl (eg. methyl), aryl C_{1-6} alkyl (eg. benzyl), aryl (eg. phenyl optionally substituted by one or more OMe or isopropyl SO_2 groups) or heteroaryl (eg. thienyl).

When present, R^3 is preferably halogen (eg. chlorine) or polyhalo C_{1-6} alkyl (eg. 2- CF_3),
 25 more preferably chlorine (eg. 2-chlorine).

When b is 0, a is preferably 1, when b is 1, a is preferably 0, 1 or 2 and when b is 2, a is preferably 0.

More preferred compounds of formula (I) are those wherein a is 1 and b is 0 or 1 or a is 0 and b is 1.

30 Especially preferred compounds of formula (I) are those wherein a is 1 and b is 0.

Preferably, ----- is a single bond.

Preferably, n represents 0 or 1, more preferably 0.

Preferably, $-O-R^4$ is present on the phenyl group at the 4-position.

When R^4 represents a group of formula (i), preferably, f represents 0, h represents 1, g represents 2, k represents 0 and R^{13} represents C_{1-6} alkyl (eg. isopropyl) or C_{3-8} cycloalkyl (eg. cyclobutyl). More preferably, when R^4 represents a group of formula (i), f represents 0, h represents 1, g represents 2, k represents 0 and R^{13} represents C_{3-8} cycloalkyl (eg. cyclobutyl).
 35

Preferably, R^4 represents $-(CH_2)_q-NR^{11}R^{12}$.

40 Preferably, q is 3.

Preferably, $NR^{11}R^{12}$ represents a heterocyclic group, more preferably unsubstituted piperidine.

Preferred compounds according to the invention include examples E1-E65 as shown below, or a pharmaceutically acceptable salt thereof.

- 5 More preferred compounds according to the invention include:
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]isoindoline;
 N-[4-(3-Piperidin-1-ylpropoxy)-benzoyl]-5-fluoroisoindoline;
 N-{4-[(1-Cyclobutyl-4-piperidinyloxy]benzoyl}isoindoline; and
 N-{4-[(1-Cyclobutyl-4-piperidinyloxy]benzoyl}-5-fluoro-isoindoline;
 10 or a pharmaceutically acceptable salt thereof.

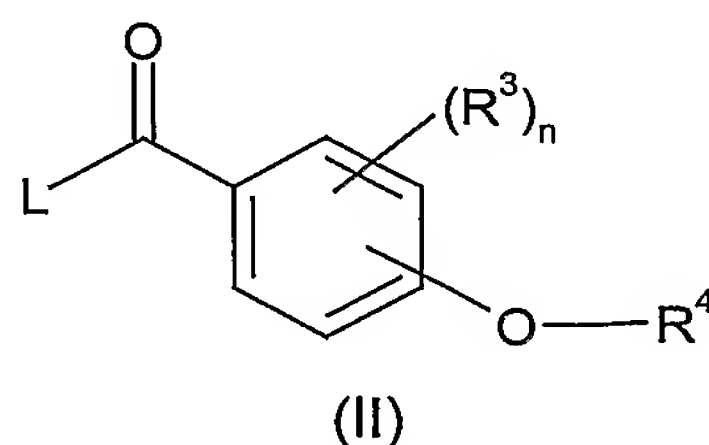
An especially preferred compound according to the invention is N-[4-(3-piperidin-1-ylpropoxy)benzoyl]isoindoline or a pharmaceutically acceptable salt thereof.

- 15 Compounds of formula (I) may form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphate, citric, lactic, mandelic, tartaric and methanesulphonic. Salts, solvates and hydrates of histamine H3 receptor antagonists or inverse agonists therefore form an aspect of the invention.

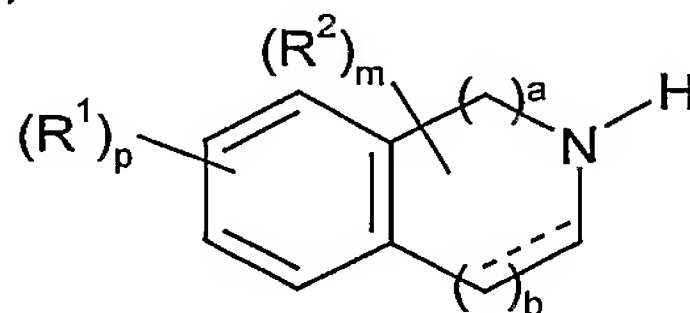
- 20 Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates. Tautomers also form an aspect of the invention.

- 25 The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

- (a) reacting a compound of formula (II)
 30



with a compound of formula (III)

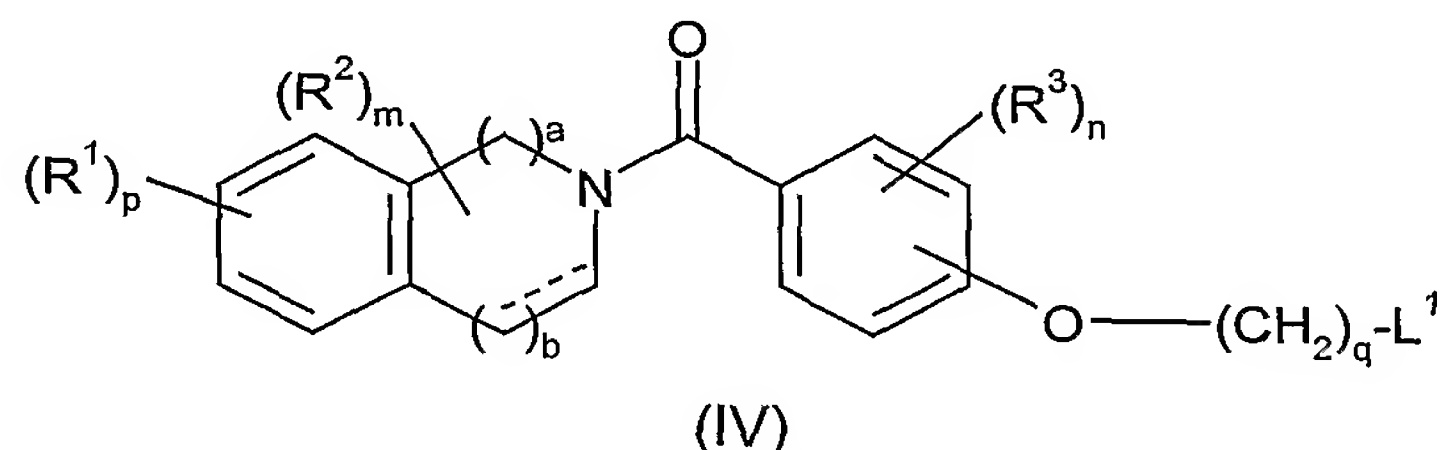


35

(III)

or a protected derivative thereof, wherein R^1 , R^2 , R^3 , R^4 , a , b , m , n and p are as defined above and L is OH or a suitable leaving group (eg. a halogen atom such as chlorine); or

(b) preparing a compound of formula (I) wherein R^4 represents $-(CH_2)_q-NR^{11}R^{12}$ which comprises reacting a compound of formula (IV)



wherein R^1 , R^2 , R^3 , a , b , m , n , p and q are as defined above and L^1 represents a suitable leaving group such as a halogen atom (eg. bromine) with a compound of formula $HNR^{11}R^{12}$; wherein R^{11} and R^{12} are as defined above; and optionally thereafter

(c) deprotecting a compound of formula (I) which is protected; and optionally thereafter

(d) interconversion to other compounds of formula (I).

Process (a) typically comprises halogenation of the compound of formula (II) with a suitable halogenating agent (eg. thionyl chloride) followed by reaction with the compound of formula (III) in the presence of a suitable base such as triethylamine or a solid supported amine, in a suitable solvent such as dichloromethane. Process (a) may also typically comprise activation of the compound of formula (II) with a coupling reagent such as dicyclohexylcarbodiimide or solid supported carbodiimide in a suitable solvent such as N,N-dimethylformamide followed by reaction with the compound of formula (III). Alternatively process (a) may involve activation of (II) by formation of a suitable ester such as a pentachlorophenyl ester followed by reaction with an N-benzyl protected analogue of (III) in the presence of poly(methylhydrosiloxane) and palladium hydroxide in a suitable solvent such as isopropanol.

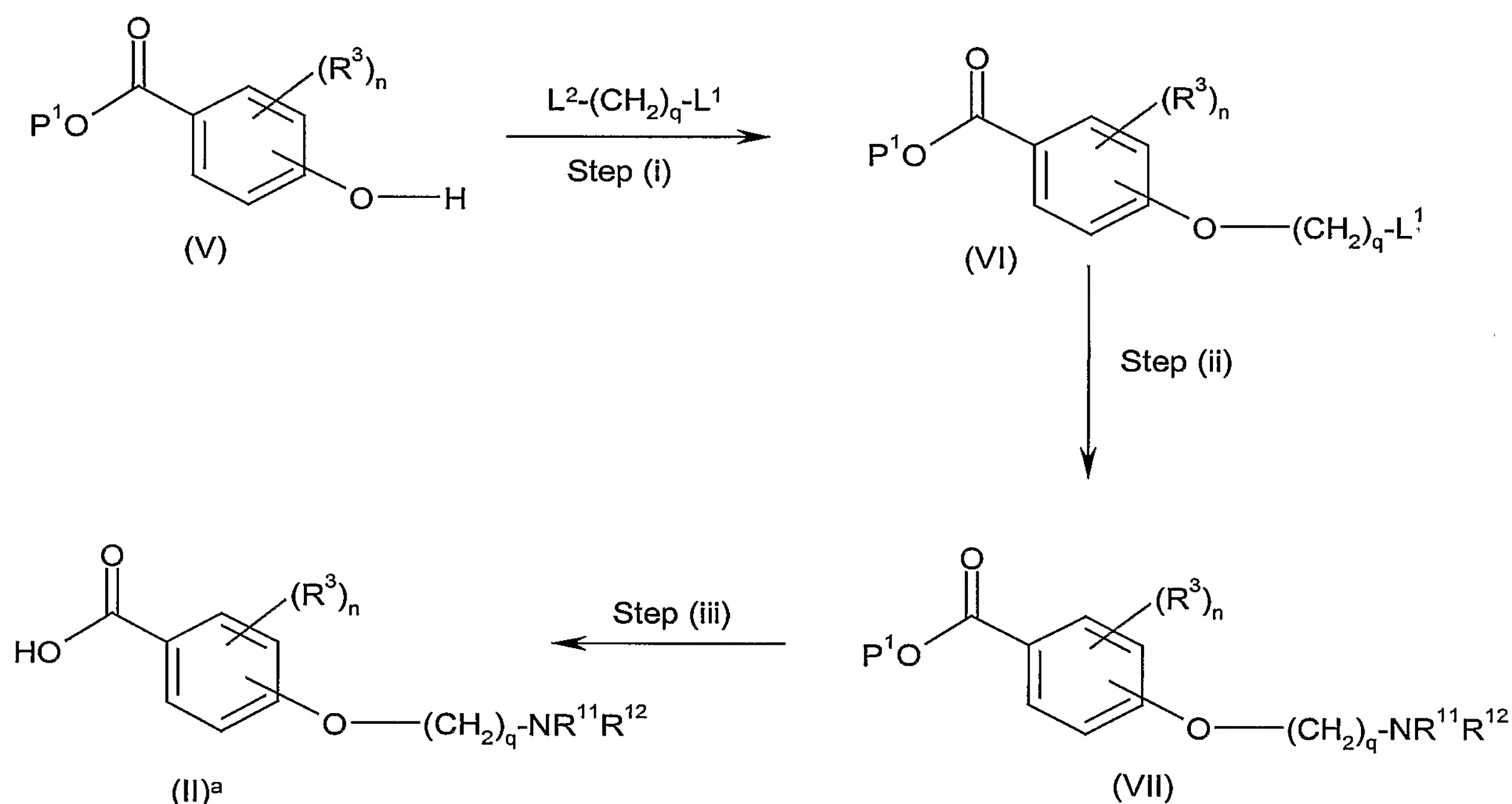
Process (b) is typically performed in the presence of a suitable solvent (such as 1-butanol) at an elevated temperature.

In process (c), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl

(e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-COCF₃) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

- 10 Process (d) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis or amide bond formation.

- 15 Compounds of formula (II) wherein R⁴ represents -(CH₂)_q-NR¹¹R¹² may be prepared in accordance with the following procedure:



- 20 wherein R³, n, q, R¹¹ and R¹² are as defined above, P¹ represents a protecting group such as methyl, ethyl or t-butyl, L¹ and L² independently represent a leaving group such as halogen (eg. L¹ represents chlorine and L² represents bromine). The -CO₂H group of compounds of formula (II)^a may be converted to -COL wherein L represents a leaving group by, for example, halogenation using thionyl chloride.

Step (i) typically comprises reaction of a compound of formula (V) with a suitable alkylating agent such as 1-bromo-3-chloropropane in a suitable solvent such as acetone in the presence of potassium carbonate.

- 5 Step (ii) typically comprises treatment of a compound of formula (VI) with an amine of formula $\text{HNR}^{11}\text{R}^{12}$.

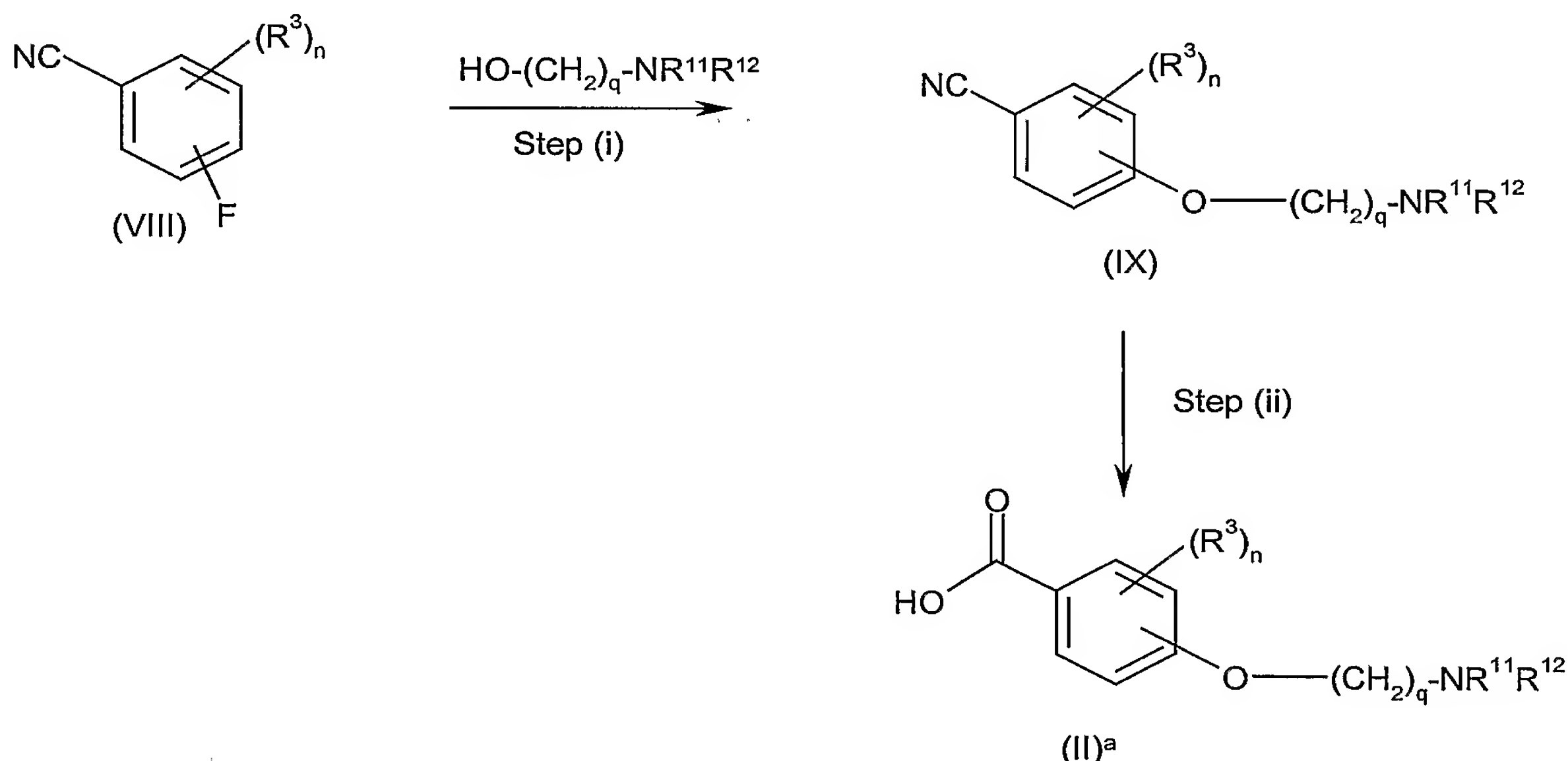
Step (iii) comprises a deprotection reaction which may be performed for example under acidic conditions with hydrochloric acid.

10

Compounds of formula (IV) may be prepared by hydrolysing a compound of formula (VI) as defined above under suitable conditions (eg. under acidic conditions with HCl), suitably activated (eg. by conversion into the acid chloride with thionyl chloride), followed by treatment with a compound of formula (III) as defined above.

15

Compounds of formula (II) wherein R^4 represents $-(\text{CH}_2)_q-\text{NR}^{11}\text{R}^{12}$ may also be prepared in accordance with the following procedure:



- 20 wherein R^3 , n , q , R^{11} and R^{12} are as defined above.

Step (i) typically comprises reaction of a compound of formula (VIII) in the presence of a suitable base such as sodium hydride in an appropriate solvent such as dimethylsulfoxide or N,N-dimethylformamide.

25

Step (ii) typically comprises a hydrolysis reaction for example under acidic conditions using hydrochloric acid.

Compounds of formula (IV) may be prepared using an analogous procedure using HO-(CH₂)_q-L³, wherein q is as defined above and L³ represents an OH group or a group convertible to a leaving group.

- 5 Compounds of formula (II) wherein R⁴ represents a group of formula (i) may be prepared in a similar manner to the procedure shown above.

Compounds of formula (III), (V) and (VIII) are either known in the literature or can be prepared by analogous methods.

10

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for and are antagonists and/or inverse agonists of the histamine H₃ receptor and are believed to be of potential use in the treatment of neurological diseases including

15

impairment, cognitive deficit, epilepsy, neuropathic pain, inflammatory pain, migraine, Parkinson's disease, multiple sclerosis, stroke and sleep disorders including narcolepsy; psychiatric disorders including schizophrenia (particularly cognitive deficit of schizophrenia), attention deficit hyperactivity disorder, depression and addiction; and other diseases including obesity, asthma, allergic rhinitis, nasal congestion, chronic

20

obstructive pulmonary disease and gastro-intestinal disorders.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance in the treatment or prophylaxis of the above disorders, in particular cognitive impairments in diseases such

25

as Alzheimer's disease and related neurodegenerative disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

30

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders.

35

When used in therapy, the compounds of formula (I) are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

40

Thus, the present invention further provides a pharmaceutical composition for use in the treatment of the above disorders which comprises the compound of

formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

5 The present invention further provides a pharmaceutical composition which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

10 Compounds of formula (I) may be used in combination with other therapeutic agents, for example histamine H1 antagonists or medicaments claimed to be useful as either disease modifying or symptomatic treatments of Alzheimer's disease. Suitable examples of such other therapeutic agents may be agents known to modify cholinergic transmission such as 5-HT₆ antagonists, M1 muscarinic agonists, M2 muscarinic antagonists or acetylcholinesterase inhibitors. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either
15 sequentially or simultaneously by any convenient route.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.
20

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such
25 combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease
30 state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral,
35 parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

40 Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting lubricants,

disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1 (Method A)

Ethyl 4-(3-Piperidin-1-ylpropoxy)benzoate (D1)

A stirred mixture of ethyl 4-(3-chloropropoxy)benzoate (4.73g) (D.A. Walsh *et al* J. Med. Chem. 1989, **32**(1), 105), piperidine (2.9ml), sodium carbonate (3.1g) and potassium iodide (162mg) in 1-butanol (50ml) was heated at 105°C for 16h. The reaction was cooled to rt, diluted with EtOAc (100ml), washed with water (3x50ml), saturated brine

(50ml), dried (MgSO_4) and evaporated to give the title compound (D1) (6.88g). MS electrospray (+ion) 292 (MH^+). ^1H NMR δ (CDCl_3): 7.98 (2H, d, $J=8.8\text{Hz}$), 6.90 (2H, d, $J=8.8\text{Hz}$), 4.34 (2H, q, $J=7.5\text{Hz}$), 4.06 (2H, t, $J=6.3\text{Hz}$), 2.46 (4H, m), 2.00 (2H, m), 1.50 (6H, m), 1.38 (3H, t, $J=7.5\text{Hz}$).

5

Description 1 (Method B)**Ethyl 4-(3-Piperidin-1-ylpropoxy)benzoate (D1)****Step 1: Ethyl 4-(3-chloropropoxy)benzoate**

10 Ethyl 4-hydroxybenzoate (60.0g), 1-bromo-3-chloropropane (71.37ml) and potassium carbonate (149.61g) were heated under reflux in acetone (1445ml) overnight. The reaction mixture was then allowed to cool to rt, filtered and evaporated. The residue was chromatographed [silica gel; step gradient 0-5% ethyl acetate/hexane]. Fractions containing pure product were combined and evaporated to give the subtitled compound as a clear oil (70.0g). MS electrospray (+ion) 243 (MH^+). ^1H NMR δ (CDCl_3): 8.00 (2H, d, $J=8.8\text{Hz}$), 6.92 (2H, d, $J=8.8\text{Hz}$), 4.36 (2H, q, $J=7.1\text{Hz}$), 4.18 (2H, t, $J=5.8\text{Hz}$), 3.74 (2H, t, $J=6.2$), 2.25 (2H, m), 1.37 (3H, t, $J=7.1\text{Hz}$).

15

Step 2: Ethyl 4-(3-Piperidin-1-ylpropoxy)benzoate

20 A stirred mixture of ethyl 4-(3-chloropropoxy)benzoate (70.0g), piperidine (43.35ml), sodium carbonate (45.36g) and potassium iodide (2.37g) in 1-butanol (650ml) was heated at 105°C for 16h. The reaction was cooled to rt, diluted with EtOAc (1600ml), washed with water (3x700ml), saturated brine (700 ml), dried (MgSO_4) and evaporated to give the title compound (D1) (82.57g) which displayed MS and ^1H NMR spectra that were identical to those of the product obtained by D1 (Method A).

25

Description 2 (Method A)**4-(3-Piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2)**

30 A solution of ethyl 4-(3-piperidin-1-ylpropoxy)benzoate (D1) (1.4g) in concentrated hydrochloric acid (15ml) was heated under reflux for 1h, cooled and evaporated to give the title compound (D2) (1.02g). MS electrospray (+ion) 264 (MH^+). ^1H NMR δ ($\text{DMSO}-d_6$): 10.59 (1H, s), 10.25 (1H, s), 7.90 (2H, d, $J=9\text{Hz}$), 7.02 (2H, d, $J=9\text{Hz}$), 4.14 (2H, t, $J=6\text{Hz}$), 3.05-3.52 (4H, m), 2.91 (2H, m), 2.20 (2H, m), 1.25-1.91 (6H, m).

Description 2 (Method B)**4-(3-Piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2)**

35 A solution of ethyl 4-(3-piperidin-1-ylpropoxy)benzoate (D1) (82.57g) in concentrated hydrochloric acid (750ml) was heated under reflux for 2h. The mixture was cooled to rt then chilled to 5°C and filtered. The filter cake was washed with acetone and dried to yield the title compound (D2) as a white crystalline solid (75.30g) that displayed MS and ^1H NMR spectra that were identical to those of the product obtained by D2 (Method A).

40

Description 3**4-(3-Piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3)**

Description 12**N-t-Butoxycarbonyl-5-methoxycarbonylisoindoline (D12)**

A mixture of di t-butyldicarbonate (0.9g) and N-benzyl-5-methoxycarbonylisoindoline (D11) (200mg) in EtOH (10ml) at rt was treated with poly(methylhydrosiloxane) (0.67ml) and palladium hydroxide on carbon (50mg, 20% Pd) and stirred overnight. The mixture was filtered and evaporated. The residue was chromatographed on a silica gel flash column [step gradient 5-20% EtOAc in light petroleum 40-60] to give the title compound (D12) (0.64g). MS electrospray (+ion) 278 (MH⁺). ¹H NMR δ (CDCl₃): 7.94 (2H, m), 7.32 (1H, m), 4.72 (2H, s), 4.68 (2H, s), 3.92 (3H, s), 1.52 (9H, s).

Description 13**N-t-Butoxycarbonyl-5-carboxyisoindoline (D13)**

A solution of N-t-butoxycarbonyl-5-methoxycarbonylisoindoline (D12) (2.11g) in MeOH (10ml) was treated with 1M NaOH and heated at 60°C for 1h. The mixture was cooled to rt and the MeOH evaporated. The aqueous was washed with diethyl ether (2x20ml), then acidified with 5% citric acid solution and extracted with diethyl ether (2x20ml). The combined extracts were washed with water (2x20ml), brine (20ml), dried (MgSO₄) and evaporated to give the title compound (D13) (1.47g). MS electrospray (+ion) 264 (MH⁺). ¹H NMR δ (CDCl₃): 8.02 (2H, m), 7.35 (1H, m), 4.75 (2H, s), 4.71 (2H, s), 1.53 (9H, s).

Description 14**N-t-Butoxycarbonyl-5-aminocarbonylisoindoline (D14)**

A mixture of N-t-butoxycarbonyl-5-carboxyisoindoline (D13) (240mg), EDC (350mg), HOBT (140mg), triethylamine (0.32ml) and 0.880 ammonia solution (1ml) in DMF (10ml) was stirred overnight at rt and then evaporated. The residue was partitioned between EtOAc (10ml) and 5% citric acid (10ml). The organic layer was collected, washed with water (10ml), saturated NaHCO₃ solution (10ml), water (10ml), brine (10ml), dried (MgSO₄) and evaporated to give the title compound (D14) (154mg). MS electrospray (+ion) 263 (MH⁺). ¹H NMR δ (CDCl₃): 7.73 (2H, m), 7.26 (1H, m), 6.88 (2H, m), 4.72 (2H, s), 4.69 (2H, s), 1.52 (9H, s).

Description 15**N-t-Butoxycarbonyl-5-cyanoisoindoline (D15)**

A solution of N-t-butoxycarbonyl-5-aminocarbonylisoindoline (D14) (140mg) in pyridine (3ml) at rt was treated with 4-toluenesulfonyl chloride (305mg) and then stirred overnight. Following evaporation the residue was dissolved in EtOAc (10ml), washed with saturated NaHCO₃ solution (10ml), water (10ml), brine (10ml), dried (MgSO₄) and concentrated. The residue was chromatographed on a silica gel flash column [step gradient 5-20% EtOAc in light petroleum 40-60] to give the title compound (D15) (0.64g). MS electrospray (+ion) 189 (MH⁺-t-Bu). ¹H NMR δ (CDCl₃): 7.56 (2H, m), 7.38 (1H, m), 4.71 (4H, m), 1.52 (9H, s).

successively with a saturated solution of potassium carbonate (1L) and water (0.5L). The organic extract was dried (MgSO_4), concentrated to a volume of 0.5L and cooled in ice. The unwanted precipitate was filtered off and the filtrate evaporated to a residue which was purified by chromatography over silica gel eluting with a gradient of dichloromethane/ethyl acetate to give the title compound (D7) as an oil (49.3g). MS electrospray (+ion) 228 (MH^+). ^1H NMR δ (CDCl_3): 7.24-7.42 (5H, m), 7.07-7.12 (1H, m), 6.82-6.89 (2H, m), 3.89 (6H, br, s).

Description 8

10 **5-Fluoroisoindoline hydrochloride (D8)**

A suspension of 20% palladium hydroxide on carbon (4.0g) and N-benzyl-5-fluoroisoindoline (D7) (44.6g) in ethanol (475ml) and conc. hydrochloric acid (d = 1.18, 25ml) was stirred with hydrogen at 50 psi for 18h at 45°C. The mixture was cooled to ambient temperature and filtered to remove the catalyst. The filtrate was evaporated *in vacuo* to give a solid which was stirred with acetone (300ml) for 0.5h and filtered to give the title compound (D8) as a solid (29.3g). ^1H NMR δ ($\text{D}_6\text{-DMSO}$): 10.0 (2H, br, s), 7.41-7.46 (1H, m), 7.15-7.29 (2H, m), 4.49 (2H, s), 4.46 (2H, s).

Description 9

20 **N-Benzyl-4-fluoroisoindoline (D9)**

3-Fluoroxylene (5.67g) was converted to the title compound (D9) (5g) using the method described in D7 for N-benzyl-5-fluoroisoindoline. MS electrospray (+ion) 228 (MH^+). ^1H NMR δ (CDCl_3): 6.82-7.42 (8H, m), 3.99 (2H, s), 3.95 (2H, s), 3.91 (2H, s).

25 Description 10

Pentachlorophenyl 4-(3-piperidin-1-ylpropoxy)benzoate (D10)

A stirred suspension of 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (1g) in DCM (10ml) at rt was treated with oxalyl chloride (0.58ml) and 10% DMF in DCM (3 drops). After 1h the solution was evaporated and then re-evaporated from DCM (2x10ml). The acid chloride was redissolved in DCM (20ml) and treated with pentachlorophenol (0.89g) and triethylamine (1.02ml), then stirred for 4h and evaporated. The residue was redissolved in EtOAc (20ml), washed with 5% sodium carbonate solution (10ml), water (2x10ml), brine (10ml), dried (MgSO_4) and evaporated to yield the title compound (D10) (1.2g). MS electrospray (+ion) 228 (MH^+). ^1H NMR δ (CDCl_3): 6.82-7.42 (8H, m), 3.99 (2H, s), 3.95 (2H, s), 3.91 (2H, s).

Description 11

N-Benzyl-5-methoxycarbonylisoindoline (D11)

4-Methoxycarbonylxylene (5.16g) was converted to the title compound (D11) (4.5g) using the method described in D7 for N-benzyl-5-fluoroisoindoline. MS electrospray (+ion) 268 (MH^+). ^1H NMR δ (CDCl_3): 7.14-7.91 (8H, m), 3.96 (2H, s), 3.92 (2H, s), 3.89 (2H, s)

4-(3-Piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (0.23g) in thionyl chloride (5ml) was heated under reflux for 1h. The reaction mixture was then evaporated to a minimum and co-evaporated from DCM (3 x 10ml) to give the title compound (D3) as a white powder (0.24g).

5

Description 4**4-(3-Piperidin-1-yl-propoxy)-2-trifluoromethyl-benzonitrile (D4)**

4-Fluoro-2-trifluoromethyl-benzonitrile (1.20g) was dissolved in THF (20 ml) and 3-piperidin-1-yl-propan-1-ol (0.91 ml) was added. The reaction was cooled to 0°C and
10 potassium hexamethyldisilazide (0.5M solution in toluene; 12.72 ml) was added dropwise. The reaction was stirred at rt overnight, then diluted with ethyl acetate (50 ml) and partitioned with aqueous 1N HCl (50 ml). The aqueous layer was washed with ethyl acetate (50 ml), then basified to pH 8.0 with sodium hydrogen carbonate and extracted with ethyl acetate (3x75 ml). The combined organic extracts were dried (MgSO₄) and
15 evaporated to give the title compound (D4) as a clear oil which crystallised on standing (0.80g).

Description 5**4-(3-Piperidin-1-yl-propoxy)-2-trifluoromethyl-benzoic acid (D5)**

4-(3-Piperidin-1-yl-propoxy)-2-trifluoromethyl-benzonitrile (D4) (0.80 g) was dissolved in
20 conc. HCl (20 ml) and heated at 135°C for 24 h. Concentrated sulfuric acid (10 ml) was added and the reaction heated at 135°C for 36h. The reaction mixture was then evaporated to a minimum and treated with 12.5 N sodium hydroxide solution until pH 12 was obtained. The mixture was filtered and the filtrate evaporated to a minimum. Conc.
25 HCl was then added until pH 1. The mixture was evaporated and the solid residue was extracted several times with methanol. The combined extracts were evaporated to give the title compound (D5) as a white solid (0.90g).

Description 6**4-(3-Piperidin-1-yl-propoxy)-2-trifluoromethyl-benzoyl chloride (D6)**

4-(3-Piperidin-1-yl-propoxy)-2-trifluoromethyl-benzoic acid (D5) (0.9 g) was heated at reflux in thionyl chloride (20 ml) for 2h. The reaction mixture was evaporated to a minimum then co-evaporated with DCM (3x) to give the title compound (D6) as a white solid (1.0g)

35

Description 7**N-Benzyl-5-fluoroisoindoline (D7)**

A solution of benzylamine (64.3ml) and triethylamine (164ml) in toluene (1L) was added to 1,2-bis(bromomethyl)-4-fluorobenzene (164.1g) (*J. Org. Chem.*, 1988, **53**, 1775-9).
40 This mixture was heated to reflux for 4h under argon. The reaction mixture was then filtered and the solid was washed with toluene (3x150ml). The filtrate was evaporated *in vacuo* and the residue dissolved in dichloromethane (1L). This solution was washed

Description 16**5-Cyanoisoindoline trifluoroacetate (D16)**

5 A solution of N-t-butoxycarbonyl-5-cyanoisoindoline (D15) (130mg) in DCM (3ml) at rt was treated with TFA (1ml) and after 1h it was evaporated. The residue was re-evaporated from MeOH / toluene to give the title compound (D16) (140mg). ¹H NMR δ (CDCl₃): 7.70 (2H, m), 7.50 (1H, m), 4.75 (4H, m).

Description 17**10 N-t-Butoxycarbonyl-5-[(pyrrolidin-1-yl)carbonyl]isoindoline (D17)**

A mixture of N-t-butoxycarbonyl-5-carboxyisoindoline (D13) (300mg), EDC (440mg), HOAT (10mg), triethylamine (0.4ml) and pyrrolidine (0.11ml) in DCM (10ml) was stirred overnight and then evaporated. The residue was redissolved in EtOAc (10ml), washed with saturated NaHCO₃ solution (10ml), water (10ml), brine (10ml), dried (MgSO₄) and
15 evaporated. The residue was chromatographed on a silica gel flash column [step gradient 70-90% EtOAc in light petroleum 40-60] to give the title compound (D17) (314mg). MS electrospray (+ion) 317 (MH⁺). ¹H NMR δ (CDCl₃): 7.42 (2H, m), 7.27 (1H, m), 4.70 (2H, m), 4.67 (2H, m), 3.65 (2H, m), 3.42 (2H, m), 1.92 (4H, m), 1.52 (9H, s).

20 Description 18**5-[(Pyrrolidin-1-yl)carbonyl]isoindoline hydrochloride (D18)**

A solution of N-t-butoxycarbonyl-5-[(pyrrolidin-1-yl)carbonyl]isoindoline (D17) (300mg) in DCM (5ml) at rt was treated with 4M HCl in dioxan (1ml) for 1h and then evaporated. The residue was triturated with acetone to give the title compound (D18) (85mg). MS
25 electrospray (+ion) 217 (MH⁺). ¹H NMR δ (DMSO-d₆): 9.95 (1H, m), 7.58 (3H, m), 4.52 (2H, m), 3.46 (2H, m), 1.84 (4H, m).

Description 19**N-t-Butoxycarbonyl-5-[(morpholin-4-yl)carbonyl]isoindoline (D19)**

30 A mixture of N-t-butoxycarbonyl-5-carboxyisoindoline (D13) (300mg), EDC (440mg), HOAT (10mg), triethylamine (0.4ml) and morpholine (0.12ml) in DCM (10ml) was stirred overnight and then evaporated. The residue was redissolved in EtOAc (10ml), washed with saturated NaHCO₃ solution (10ml), water (10ml), brine (10ml), dried (MgSO₄) and
35 evaporated. The residue was chromatographed on a silica gel flash column [step gradient 70-90% EtOAc in light petroleum 40-60] to give the title compound (D19) (314mg). MS electrospray (+ion) 333 (MH⁺). ¹H NMR δ (CDCl₃): 7.30 (3H, m), 4.70 (2H, m), 4.67 (2H, m), 3.70 (8H, m), 1.52 (9H, s).

Description 20**40 5-[(Morpholin-4-yl)carbonyl]isoindoline trifluoroacetate (D20)**

A solution of N-t-butoxycarbonyl-5-[(morpholin-4-yl)carbonyl]isoindoline (D19) (300mg) in DCM (5ml) at rt was treated with TFA (2ml) for 1h and then evaporated. The residue

was re-evaporated from DCM / toluene to give the title compound (D20) (305mg). MS electrospray (+ion) 233 (MH⁺). ¹H NMR δ (CDCl₃): 10.10 (1H, m), 7.25 (3H, m), 4.64 (2H, m), 4.53 (2H, m), 3.54 (8H, m).

5 Description 21

4-[(1-tert-Butoxycarbonyl-4-piperidinyloxy]benzonitrile (D21)

4-Fluorobenzonitrile (3.0g) was dissolved in THF (50ml) and then N-tert-butoxy-carbonyl-4-piperidinol (4.98g) was added. Potassium hexamethyldisilazide (20% wt solution in THF, 24.62g) was then added dropwise and the reaction stirred at rt for 2h. The reaction mixture was then evaporated to a minimum, redissolved in EtOAc (100 ml) and washed with aqueous 1N HCl (2x100 ml), saturated sodium bicarbonate solution (2x100 ml) and brine (100 ml). The organic layer was dried (MgSO₄) and then purified by chromatography [silica gel, step gradient 0-60% EtOAc/Hexane]. Fractions containing the required product were evaporated to give the title compound (D21) as a clear oil which crystallised on standing (6.83 g). ¹H NMR δ (CDCl₃): 7.59 (2H, d, J=7.50Hz), 6.95 (2H, d, J=7.50Hz), 4.44 (1H, m), 3.70 (2H, m), 3.38 (2H, m), 1.91 (2H, m), 1.77 (2H, m), 1.47 (9H, s).

Description 22

4-(4-Piperidinyloxy)benzonitrile trifluoroacetate (D22)

4-[(1-tert-Butoxycarbonyl-4-piperidinyloxy]benzonitrile (D21) (6.83g) was dissolved in DCM (30ml) and TFA (30 ml) was added. The reaction was stirred at rt for 1h and then evaporated to give the title compound (D22) as a yellow oil (7.15g – TFA salt plus 1.3 equivalents of TFA).

Description 23

4-[(1-Cyclobutyl-4-piperidinyloxy]benzonitrile (D23)

4-(4-Piperidinyloxy)benzonitrile trifluoroacetate (D22) (2.2g) was dissolved in DCM (50ml) and triethylamine (1.92ml) was added followed by cyclobutanone (0.64g). The mixture was stirred for 5min, then sodium triacetoxyborohydride (1.94g) was added and the reaction was stirred at rt under argon overnight. The reaction mixture was then washed with saturated potassium carbonate solution (3x30ml) and brine (30ml). The organic layer was dried (MgSO₄) and evaporated to give the title compound (D23) as a white solid (1.91g). ¹H NMR δ (CDCl₃): 7.56 (2H, d, J=6.84Hz), 6.93 (2H, d, J=6.80Hz), 4.41 (1H, m), 2.77 (1H, m), 2.75 (2H, m), 2.30 (2H, m), 2.06 (4H, m), 1.87 (4H, m), 1.66 (2H, m).

Description 24

4-[(1-Cyclobutyl-4-piperidinyloxy]benzoic acid hydrochloride (D24)

4-[(1-Cyclobutyl-4-piperidinyloxy]benzonitrile (D23) (1.91g) was dissolved in conc. HCl (30ml) and heated to 120°C for 2h. The reaction mixture was then allowed to cool to rt and then further cooled to 5°C. The resultant white precipitate was filtered off and

washed with a small quantity of water. The solid was then dried at 50°C under vacuum overnight to yield the title compound (D24) as a white powder (0.95g). ¹H NMR δ (DMSO-d₆): 12.60 (1H, s), 10.96 (1H, s), 7.90 (2H, d, J=8.70Hz), 7.09 (2H, d, J=8.60Hz), 4.09-4.64 (1H, m), 3.66-3.15 (3H, m), 2.99-2.77 (2H, m), 2.48-1.60 (10H, m).

5

Description 25**4-[(1-Cyclobutyl-4-piperidinyloxy)benzoyl chloride hydrochloride (D25)**

4-[(1-Cyclobutyl-4-piperidinyloxy)benzoic acid hydrochloride (D24) (0.20g) was dissolved in thionyl chloride (10 ml) and heated under reflux for 1.5h. The thionyl chloride was removed by evaporation and the residue evaporated from DCM (3x10ml) to give the title compound (D25) (0.21g).

10

Description 26**2-Chloro-4-(3-piperidin-1-ylpropoxy)benzonitrile (D26)**

2-Chloro-4-fluorobenzonitrile (5.0g) and 3-(1-piperidinyloxy)-1-propanol (3.4g) were stirred in DMSO (70 ml) at rt under argon. Sodium hydride (60% wt in mineral oil, 1.976g) was then added and the reaction stirred at rt for 5h. The reaction mixture was diluted with ethyl acetate (200ml), washed with saturated sodium hydrogen carbonate (100ml), water (3x100 ml), brine (100ml), dried (MgSO₄) and evaporated. The crude product was then purified by column chromatography [silica gel, step gradient 0-10% MeOH (containing 10% .880 ammonia solution) in DCM] and fractions containing pure product were combined and evaporated to give the title compound (D26) as a white solid (6.29g). MS electrospray (+ion) 279/281 (MH⁺).

20

Description 27**2-Chloro-4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D27)**

2-Chloro-4-(3-piperidin-1-ylpropoxy)benzonitrile (D26) (6.29g) with aqueous 1M sodium hydroxide (45.2 ml) in ethanol (60ml) was heated at reflux for 72h. The reaction mixture was then evaporated to remove ethanol and the aqueous solution treated with excess conc. hydrochloric acid and heated at 120°C for 2h. The reaction mixture was then cooled to 5°C and filtered. The filter cake was washed with a small volume of water and then acetone followed by drying at 65°C under high vacuum overnight to give the title compound (D27) as a pale brown powder (6.48g). MS electrospray (+ion) 298/230 (MH⁺). ¹H NMR δ (DMSO-d₆): 13.05 (1H, s), 10.85 (1H, s), 7.89 (1H, d, J=8.7Hz), 7.10 (1H, s), 7.02 (1H, d, J= 8.7Hz), 4.16 (2H, t, J=6.0Hz), 3.40 (2H, m), 3.13 (2H, m), 2.88 (2H, m), 2.23 (2H, m), 1.94-1.35 (6H, m).

30

35

Description 28**2-Chloro-4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D28)**

2-Chloro-4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D27) (1.0g) was heated at reflux in thionyl chloride (20ml) for 1.5h. The thionyl chloride was removed by evaporation and the residue evaporated from DCM (3x30ml) to give the title compound

40

(D28) (1.0g).

Description 29

2-Chloro-4-[(1-tert-butoxycarbonyl-4-piperidinyloxy]benzonitrile (D29)

5 The title compound (D29) was obtained as a white solid (5.0 g) using the procedure described in D21 except that 2-chloro-4-fluorobenzonitrile (2.66g) was used. ¹H NMR δ (CDCl₃): 7.57 (1H, d, J=8.72Hz), 7.01 (1H, s), 6.86 (1H, d, J=8.72Hz), 4.55 (1H, m), 3.69 (2H, m), 3.38 (2H, m), 1.93 (2H, m), 1.78 (2H, m), 1.47 (9H, s).

Description 30

2-Chloro-4-(4-piperidinyloxy)benzonitrile hydrochloride (D30)

2-Chloro-4-[(1-tert-butoxycarbonyl-4-piperidinyloxy]benzonitrile (D29) (5.0g) was dissolved in methanol (150ml) and 4N HCl in dioxane (100ml) was added. The reaction stirred at rt overnight. The reaction mixture was then evaporated to give the title
15 compound (D30) as a white solid (4.0g).

Description 31

2-Chloro-4-[(1-isopropyl-4-piperidinyloxy]benzonitrile (D31)

2-Chloro-4-(4-piperidinyloxy)benzonitrile hydrochloride (D30) (1.5g) was dissolved in
20 DCM (40ml) and triethylamine (2.29ml) was added followed by acetone (0.64g). The mixture was stirred for 5min and then sodium triacetoxyborohydride (1.94g) was added and the reaction stirred at rt under argon overnight. The reaction mixture was then washed with saturated potassium carbonate solution (2x40ml) and brine (40ml). The organic layer was dried (MgSO₄) and evaporated to give the title compound (D31) as a
25 white solid (1.51g). MS electrospray (+ion) 279 (MH⁺).

Description 32

2-Chloro-4-[(1-isopropyl-4-piperidinyloxy]benzoic acid hydrochloride (D32)

2-Chloro-4-[(1-isopropyl-4-piperidinyloxy]benzonitrile (D31) (1.51g) was dissolved in
30 conc. HCl and heated at 125°C for 72h with additional conc. HCl (10ml) added every 2h 4 times a day. The reaction mixture was then evaporated to a minimum (co-evaporated with toluene (3x30ml) then MeOH/toluene (1:1 vol, 2x30ml). The residue was dissolved in methanol and acetone was added until a precipitate (ammonium chloride) formed which was filtered off. The filtrate was evaporated to a minimum and dried at 50°C
35 under vacuum overnight to yield the title compound (D32) as a white powder (1.66g). MS electrospray (+ion) 298 (MH⁺).

Description 33

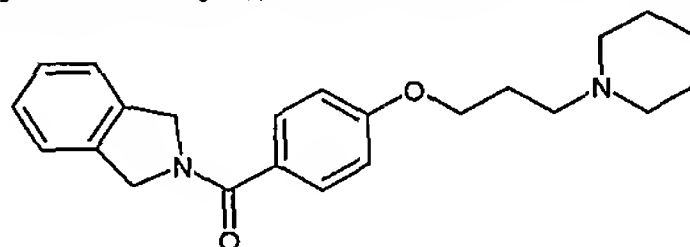
2-Chloro-4-[(1-isopropyl-4-piperidinyloxy]benzoyl chloride hydrochloride (D33)

40 2-Chloro-4-[(1-isopropyl-4-piperidinyloxy]benzoic acid hydrochloride (D32) (0.20g) was dissolved in thionyl chloride (10ml) and heated under reflux for 1.5h. The thionyl chloride was removed by evaporation and the residue was evaporated from DCM (3x10ml) to

J=6Hz), 4.04 (2H, t, J=8Hz), 2.80-3.00 (6H, m), 2.88 (2H, m), 2.20 (2H, m), 1.30-1.85 (6H, m).

Example 2 (Method A)

5 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]isoindoline hydrochloride (E2)



4-(3-Piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (150mg) was converted to the title compound (E2) by reaction with isoindoline (54mg) using the method described in Example 1 (E1) (yield = 198mg). MS electrospray (+ion) 365 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.33 (1H, s), 7.62 (2H, d, J=8.8Hz), 7.02 (2H, d, J=8.8Hz), 7.31 (4H, m), 4.86 (2H, s), 4.82 (2H, s), 4.13 (2H, t, J=6.5Hz), 2.80-3.52 (6H, m), 2.21 (2H, m), 1.30-1.85 (6H, m).

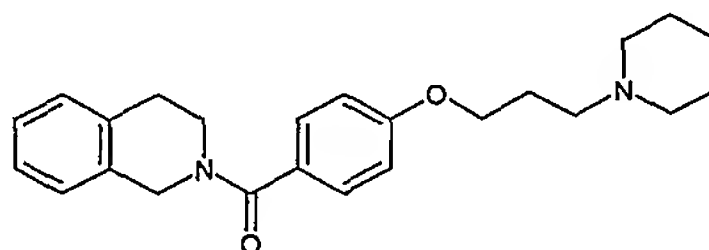
Example 2 (Method B)

15 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]isoindoline hydrochloride (E2)

A stirred suspension of 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2 (Method B); 25g) in DCM (250ml) at rt was treated with oxalyl chloride (10.92ml) and 10% DMF in DCM (1 drop). After 2h the solution was evaporated and then re-evaporated from DCM (100ml) and toluene (100ml). The acid chloride was redissolved in DCM (400ml) and treated with isoindoline hydrochloride (12.8g). The stirred mixture was cooled in ice and triethylamine (46.4ml) was added over 20min. The mixture was allowed to gain rt and stirred for 1h. The solution was washed with saturated sodium hydrogen carbonate solution (2x200ml), water (2x200ml), brine (200ml), dried (MgSO₄) and evaporated. The residue was chromatographed on a silica gel flash column [step gradient 5-9% MeOH (containing 10% .880 ammonia solution) in DCM]. Fractions containing the required product were evaporated and then re-evaporated from EtOH to give a solid (27.5g) which was redissolved in DCM (300ml), treated with 4M HCl in dioxan (28.3ml) and then evaporated. The resulting solid was crystallised from EtOH / diethyl ether to give 2 crops (28.5g). This material was recrystallised from MeOH / diethyl ether to give the title compound (E2) (26.4g).

Example 3

N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-3,4-dihydro-1H-isoquinoline hydrochloride (E3)

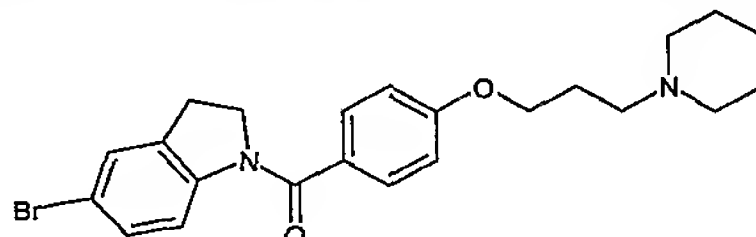


4-(3-Piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (299mg) was converted to the title compound (E3) by reaction with 1,2,3,4-tetrahydroisoquinoline (133mg) using the method described in Example 1 (E1) (yield = 376mg). MS electrospray (+ion) 379

(MH⁺). ¹H NMR δ (DMSO-d₆): 9.89 (1H, s), 7.00-7.45 (8H, m), 4.69 (2H, s), 4.11 (2H, t, J=6Hz), 3.7 (2H, m), 3.46 (2H, m), 3.18 (2H, m), 2.89 (4H, m), 2.18 (2H, m), 1.30-1.87 (6H, m).

5 Example 4

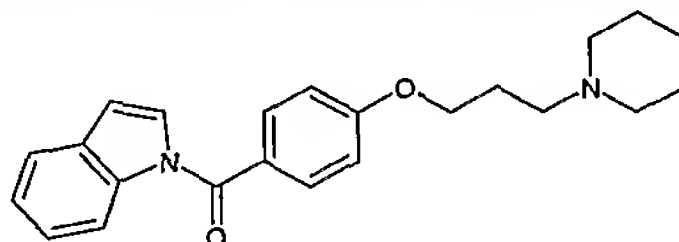
N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-5-bromoindoline hydrochloride (E4)



4-(3-Piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (299mg) was converted to the title compound (E4) by reaction with 5-bromoindoline (198mg) using the method described in Example 1 (E1) (yield = 372mg). MS electrospray (+ion) 443, 445 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.05 (1H, s), 7.01-7.82 (7H, m), 4.11 (2H, t, J=6Hz), 4.06 (2H, m), 3.46 (2H, m), 3.19 (2H, m), 3.09 (2H, m), 2.21 (2H, m), 1.30-1.87 (6H, m).

Example 5

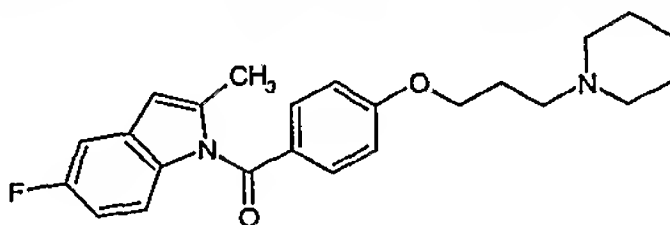
15 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]indole hydrochloride (E5)



A solution of 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (150mg) in thionyl chloride (4ml) was refluxed for 1h, cooled to rt and evaporated. The acid chloride was re-evaporated from DCM (2x3ml). The residue was redissolved in DMF (3ml) and added to an ice-cold stirred solution of indole (59mg) and sodium hydride (40mg of a 60% dispersion in oil) in DMF (2ml). The mixture was stirred for 1h then 2h at rt. Methanol (2ml) was added and the mixture evaporated. The residue was chromatographed (silica gel, step gradient 4-8% MeOH in DCM). Fractions containing the required product were treated with excess hydrogen chloride (4M solution in dioxan) and then concentrated to yield the title compound (E5) (72mg). MS electrospray (+ion) 363 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.30 (1H, s), 6.75-8.22 (10H, m), 4.20 (2H, t, J=6Hz), 2.80-3.55 (6H, m), 2.25 (2H, m), 1.25-1.91 (6H, m).

Example 6

30 5-Fluoro-2-methyl-N-[4-(3-piperidin-1-ylpropoxy)benzoyl]-indole hydrochloride (E6)



The title compound (E6) was prepared from 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) and 5-fluoro-2-methyl-indole using the method described in Example 5 (E5).

give the title compound (D33) (0.21g).

Description 34

2-Chloro-4-[(1-cyclobutyl-4-piperidinyloxy)benzonitrile (D34)

5 The title compound (D34) was obtained as a white solid (1.56g) using the procedure of D23 except that 2-chloro-4-(4-piperidinyloxy)benzonitrile hydrochloride (D30) (1.5g) was used. ¹H NMR δ (CDCl₃): 7.57 (1H, d, J=8.73Hz), 6.99 (1H, s), 6.87 (2H, d, J=8.80), 4.43 (1H, m), 2.76 (1H, m), 2.60 (2H, m), 2.28 (2H, m), 2.15-1.58 (10H, m).

10 Description 35

2-Chloro-4-[(1-cyclobutyl-4-piperidinyloxy)benzoic acid hydrochloride (D35)

2-Chloro-4-[(1-cyclobutyl-4-piperidinyloxy)benzonitrile (D34) (1.56g) was dissolved in conc. HCl and heated at 125°C for 72h with additional conc. HCl (10ml) added every 2h 4 times a day. The reaction mixture was then evaporated to a minimum (co-evaporated with toluene (3x30ml) then MeOH/toluene (1:1 vol 2x30ml). The residue was dissolved in methanol, and acetone was added until a precipitate (ammonium chloride) formed which was filtered off. The filtrate was evaporated to a minimum and dried at 50°C under vacuum overnight to yield the title compound (D35) as a white powder (1.21 g). MS electrospray (+ion) 310 (MH⁺).

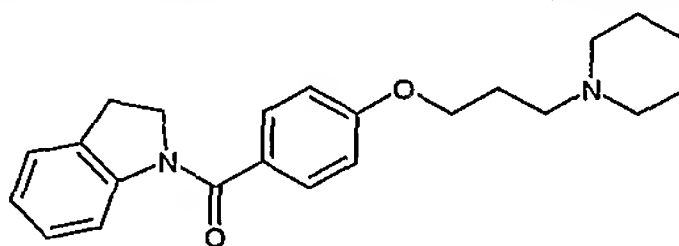
20 Description 36

2-Chloro-4-[(1-cyclobutyl-4-piperidinyloxy)benzoyl chloride hydrochloride (D36)

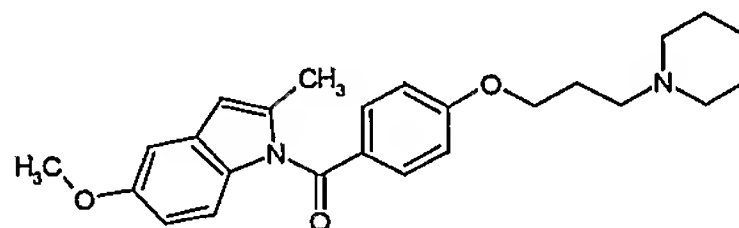
2-Chloro-4-[(1-cyclobutyl-4-piperidinyloxy)benzoic acid hydrochloride (D35) (0.20g) was dissolved in thionyl chloride (10ml) and heated under reflux for 1.5h. The thionyl chloride was removed by evaporation and the residue evaporated from DCM (3x10ml) to give the title compound (D36) (0.21 g).

Example 1

N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]indoline hydrochloride (E1)



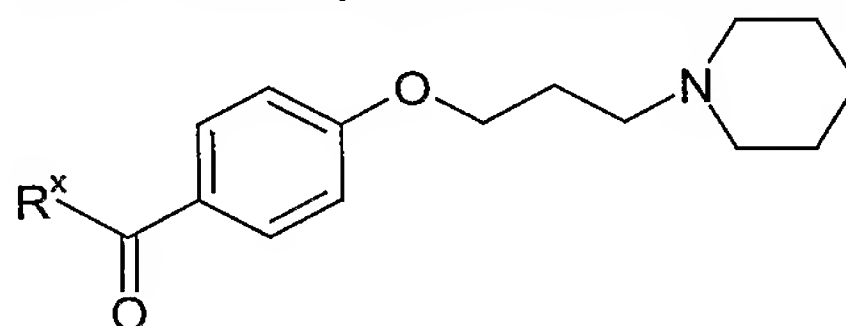
30 A solution of 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (150mg) in thionyl chloride (4ml) was refluxed for 1h, cooled to rt and evaporated. The acid chloride was re-evaporated from DCM (2x3ml). The residue was redissolved in DCM (5ml) and triethylamine (0.21ml) and added to a stirred solution of indoline (54mg) in DCM (2ml) at
35 rt. The mixture was stirred for 1h, washed with saturated sodium hydrogen carbonate solution (5ml), water (3x5ml), dried (MgSO₄) and evaporated. The residue was chromatographed (silica gel, step gradient 4-8% MeOH in DCM). Fractions containing the required product were treated with excess hydrogen chloride (4M solution in dioxan) and then concentrated to yield the title compound (E1) (126mg). MS electrospray (+ion)
40 365 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.21 (1H, s), 6.95-7.81 (8H, m), 4.14 (2H, t,

Example 7**5-Methoxy-2-methyl-N-[4-(3-piperidin-1-ylpropoxy)benzoyl]-indole hydrochloride (E7)**

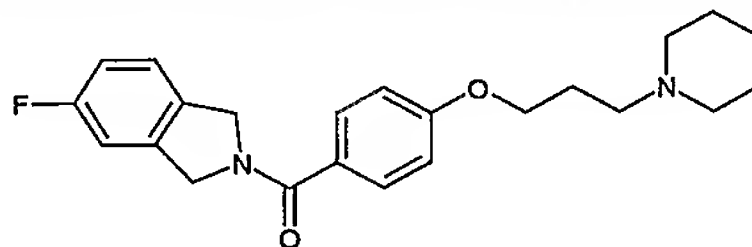
- 5 The title compound (E7) was prepared from 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) and 5-methoxy-2-methyl-indole using the method described in Example 5 (E5).

Examples 8-10 (E8-10)

- 10 Examples 8 – 10 were prepared from 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) and the appropriate amine using the method outlined in Example 1 (E1) and displayed ¹H NMR and mass spectral data that were consistent with structure.



Example No	R ^x	Mass Spectrum (ES ⁺)
E8		383 [M+H] ⁺
E9		379 [M+H] ⁺
E10		379 [M+H] ⁺

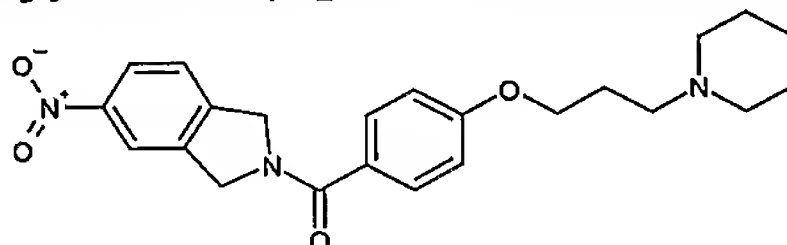
Example 11**N-[4-(3-Piperidin-1-ylpropoxy)-benzoyl]-5-fluoroisindoline hydrochloride (E11)**

- 15 A stirred mixture of 5-fluoroisindoline hydrochloride (D8) (183mg) and
 20 diethylaminoethylpolystyrene (626mg, 3.2 mmol/g) in DCM (10ml) at rt was treated with
 4-(3-piperidin-1-ylpropoxy)-benzoyl chloride hydrochloride (223mg) (D3). After 1h the
 reaction mixture was chromatographed directly [silica gel, step gradient 0-10% MeOH
 (containing 10% .880 ammonia solution) in DCM]. Fractions containing the required
 product were evaporated, redissolved in DCM, treated with excess hydrogen chloride
 25 (4M solution in dioxan) and then evaporated. The residue was triturated with acetone,
 filtered, washed with acetone and dried to yield the title compound (E11) (80mg). MS
 electrospray (+ion) 383 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.21 (1H, s), 7.61 (2H, d,

J=8.8Hz), 7.05-7.50 (3H, m), 7.01 (2H, d, J=8.8Hz), 4.81 (4H, m), 4.13 (2H, t, J=6 Hz), 3.46 (2H, m), 3.15 (2H, m), 2.88 (2H, m), 2.21 (2H, m), 1.28-1.92 (6H, m).

Example 12

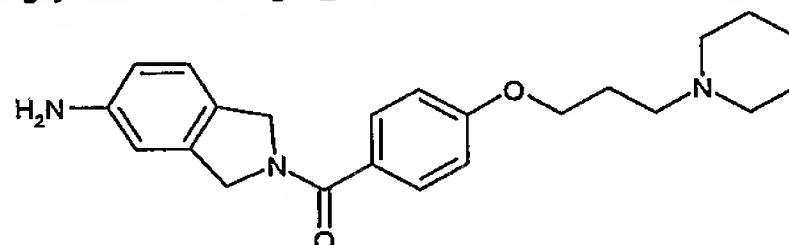
5 N-[4-(3-Piperidin-1-ylpropoxy)-benzoyl]-5-nitroisoindoline hydrochloride (E12)



An ice cold stirred mixture of 5-nitroisoindoline (2.27g) (Fraenkel, Chem Ber 1900, 33, 2811) and 4-(3-piperidin-1-ylpropoxy)-benzoyl chloride hydrochloride (3.35g) (D3) in DCM (50ml) was treated dropwise with triethylamine (5.56 ml). The reaction mixture was allowed to gain rt, stirred for 1h then washed with saturated sodium hydrogen carbonate solution (50ml), water (3x50ml), brine (50ml), dried (MgSO₄) and evaporated. Chromatography [silica gel, step gradient 0-10% MeOH (containing 10% .880 ammonia solution) in DCM] afforded the free base (2.92g). A sample (47mg) in DCM (2ml) was treated with excess 4M HCl in dioxan and evaporated to give the title compound (E12) (51mg). MS electrospray (+ion) 410 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.20 (1H, s), 8.25 (2H, m), 7.62 (3H, m), 7.03 (2H, d, J=8.8Hz), 4.95 (4H, m), 4.14 (2H, t, J=6 Hz), 3.45 (2H, m), 3.20 (2H, m), 2.90 (2H, m), 2.20 (2H, m), 1.28-1.92 (6H, m).

Example 13

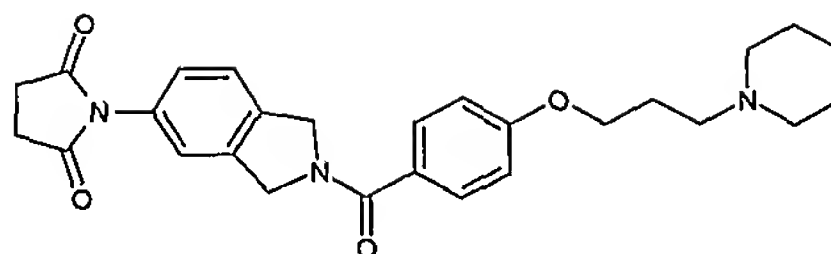
20 N-[4-(3-Piperidin-1-ylpropoxy)-benzoyl]-5-aminoisoindoline hydrochloride (E13)



A stirred solution of N-[4-(3-piperidin-1-ylpropoxy)-benzoyl]-5-nitroisoindoline (E12) (0.5g) in THF (50ml) was treated with titanium (III) chloride (5.63ml of a 30% w/v solution in hydrochloric acid). After 3h EDTA (2.85g) and water (100ml) were added and the mixture stirred for 15 min. The mixture was made basic with potassium carbonate and extracted with DCM (2x75ml). The combined extracts were dried (MgSO₄) and evaporated. Chromatography [silica gel, step gradient 0-10% MeOH (containing 10% .880 ammonia solution) in DCM] afforded the free base (430mg). A sample (25mg) in DCM (2ml) was treated with excess 4M HCl in dioxan and evaporated to give the title compound (E13) (26mg). MS electrospray (+ion) 380 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.41 (1H, s), 9.80 (2H, bs), 7.61 (2H, d, J=8.5Hz), 7.09-7.51 (3H, m), 7.03 (2H, d, J=8.5Hz), 4.85 (4H, m), 4.10 (2H, t, J=6 Hz), 3.45 (2H, m), 3.19 (2H, m), 2.91 (2H, m), 2.21 (2H, m), 1.28-1.95 (6H, m).

35 Example 14

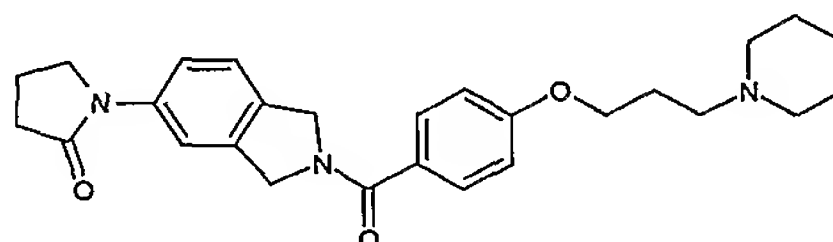
N-[4-(3-Piperidin-1-ylpropoxy)-benzoyl]-5-(1-succinimido)-isoindoline hydrochloride (E14)



A stirred mixture of succinic anhydride (79mg) and N-[4-(3-piperidin-1-ylpropoxy)-benzoyl]-5-aminoisoindoline hydrochloride (E13) (150mg) were fused at 150°C for 2h. The mixture was cooled to rt and partitioned between EtOAc (10ml) and saturated sodium hydrogen carbonate solution (10ml). The organic layer was washed with water (2x10ml), brine (10ml), dried (MgSO₄) and evaporated. The residue was dissolved in DCM, treated with excess 4M HCl in dioxan and evaporated. Crystallisation from EtOH / diethyl ether gave the title compound (E14) (90mg). MS electrospray (+ion) 462 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.15 (1H, s), 7.63 (2H, d, J=8.5Hz), 7.08-7.54 (3H, m), 7.02 (2H, d, J=8.5Hz), 4.87 (4H, m), 4.13 (2H, t, J=6 Hz), 3.09-3.52 (8H, m), 2.91 (2H, m), 2.21 (2H, m), 1.30-1.88 (6H, m).

Example 15

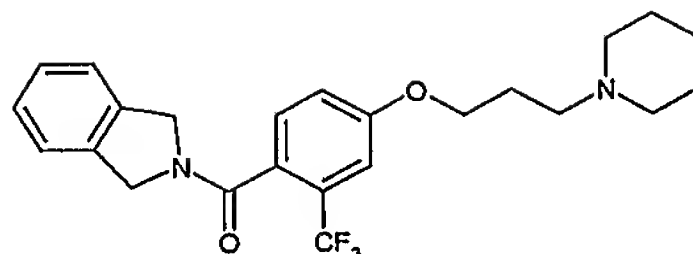
N-[4-(3-Piperidin-1-ylpropoxy)-benzoyl]-5-(2-oxo-pyrrolidin-1-yl)-isoindoline hydrochloride (E15)



A stirred mixture of diethylaminomethyl polystyrene (247mg, 3.2mmol/g) and N-[4-(3-piperidin-1-ylpropoxy)-benzoyl]-5-aminoisoindoline hydrochloride (E13) (150mg) in DCM (5ml) at rt was treated with 4-bromobutanoyl chloride (0.05ml) for 30 mins. The mixture was filtered and evaporated. The residue was redissolved in DMF (5ml) and treated with sodium hydride (18mg of a 60% suspension in mineral oil) and stirred for 2h. A further portion of sodium hydride (18 mg) was added and the mixture stirred for 1h. The reaction was partitioned between EtOAc (10ml) and saturated sodium hydrogen carbonate solution (10ml). The organic layer was washed with water (2x10ml), brine (10ml), dried (MgSO₄) and evaporated. After chromatography [silica gel, step gradient 0-10% MeOH (containing 10% .880 ammonia solution) in DCM] fractions containing the required product were evaporated, then redissolved in DCM, treated with excess 4M HCl in dioxan and evaporated. Crystallisation from EtOH / diethyl ether afforded the title compound (E15) (77mg). MS electrospray (+ion) 448 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.15 (1H, s), 7.60 (4H, m), 7.34 (1H, m), 7.0 (2H, d, J=8.5Hz), 4.80 (4H, m), 4.13 (2H, t, J=6 Hz), 3.80 (2H, m), 3.05-3.58 (6H, m), 2.91 (2H, m), 2.21 (2H, m), 2.06 (2H, m), 1.28-1.90 (6H, m).

Example 16

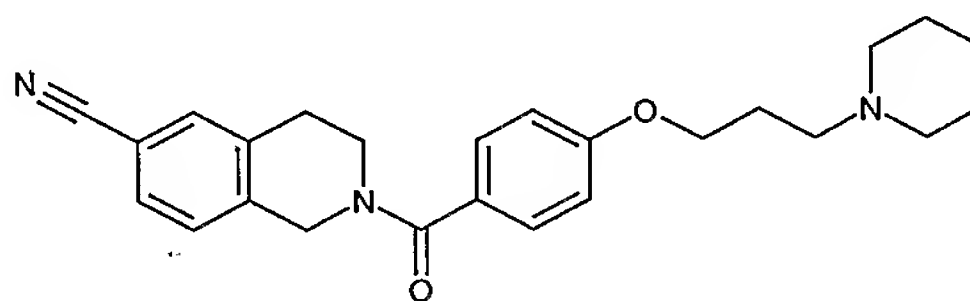
N-[4-(3-Piperidin-1-ylpropoxy)-2-trifluoromethyl-benzoyl]isoindoline hydrochloride (E16)



A solution of 4-(3-piperidin-1-ylpropoxy)-2-trifluoromethyl-benzoyl chloride (D6) (150 mg) in DCM (10ml) was added to isoindoline (0.046ml) and diethylaminomethyl polystyrene (0.60g; 3.2mmol/g). The mixture was stirred for 16h, then loaded directly onto a silica column and eluted with 0-10% MeOH (containing 10% 0.880 ammonia solution) in DCM. The isolated free base was dissolved in DCM (5ml) and treated with 4N HCl/dioxane solution (1 ml) with stirring for 10 min. The mixture was concentrated, and the residue co-evaporated with toluene (3x10ml) and then dried at 50°C under high vacuum for 16h to yield the title compound (E16) as a beige solid (0.094g). MS electrospray (+ion) 433 (MH⁺). ¹H NMR δ (DMSO-d₆): 9.96 (1H, s), 7.63 (1H, d, J=8.36 Hz), 7.46-7.23 (6H, m), 4.82 (2H, s), 4.47 (2H, s), 4.20 (2H, t, J=5.88Hz), 3.47 (2H, m), 3.19 (2H, m), 2.87 (2H, m), 2.20 (2H, m), 1.80-1.38 (6H, m).

Example 17

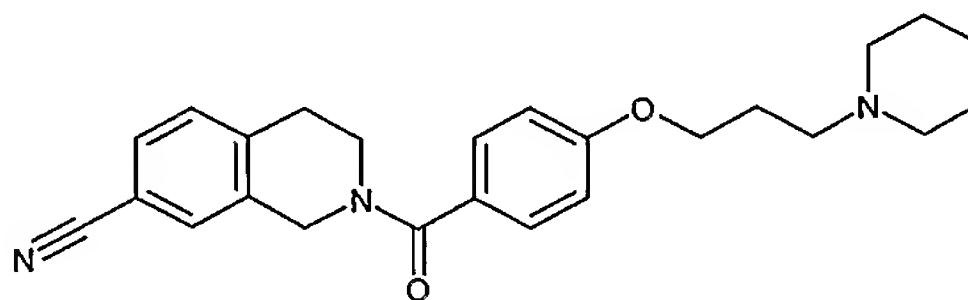
N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-6-cyano-1,2,3,4-tetrahydroisoquinoline hydrochloride (E17)



The title compound was prepared from 4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3) (0.20g) and 6-cyano-1,2,3,4-tetrahydroisoquinoline hydrochloride (WO98/50363) (0.15g) using the procedure described for Example 1 and isolated as a white solid (0.13g). MS electrospray (+ion) 404 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.20 (1H, s), 7.69 (1H, s), 7.65 (1H, d, J=7.5Hz), 7.45 (3H, m), 7.02 (2H, d, J=8.6Hz), 4.76 (1H, s), 4.11 (1H, t, J=5.9), 3.68 (2H, m), 3.44 (2H, m), 3.17 (2H, m), 2.90 (4H, m), 2.19 (2H, m), 1.78-1.37 (6H, m).

Example 18

N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-7-cyano-1,2,3,4-tetrahydroisoquinoline hydrochloride (E18)

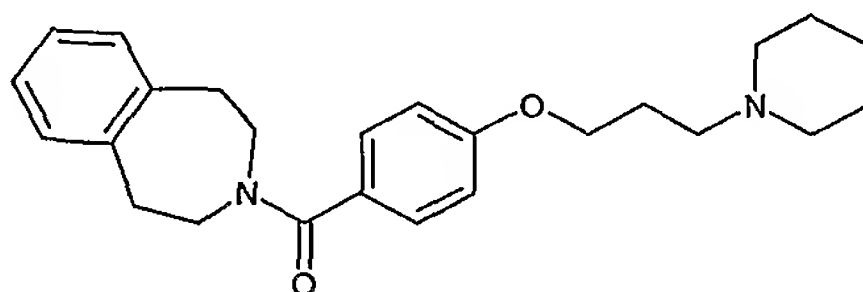


A solution of 4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3) (0.14g) in DCM (10ml) was added to 7-cyano-1,2,3,4-tetrahydroisoquinoline (WO98/50364) (0.08g) and diethylaminomethyl polystyrene (0.6g, 3.2mmol/g). The mixture was stirred for 16h then loaded directly onto a silica column and eluted with 0-10% MeOH (containing 10% 0.880 ammonia solution) in DCM. The isolated free base was dissolved in DCM (5ml)

and treated with 4N HCl/dioxane solution (1 ml) with stirring for 10min. The mixture was concentrated and the residue co-evaporated with toluene (3x10ml) then crystallised from ethanol/diethyl ether, and dried at 80°C under high vacuum for 16h to yield the title compound (E18) as a beige solid (0.03g). MS electrospray (+ion) 404 (MH⁺). ¹H NMR δ (DMSO-d₆): 9.91 (1H, s), 7.85 (1H, m), 7.65 (1H, d, J=7.9Hz), 7.42 (3H, m), 7.02 (2H, d, J=8.6), 4.73 (2H, s), 4.11 (2H, t, J=5.9 Hz), 3.68 (2H, m), 3.44 (2H, m), 3.17 (2H, m), 2.93 (4H, m), 2.20 (2H, m), 1.91-1.41 (6H, m).

Example 19

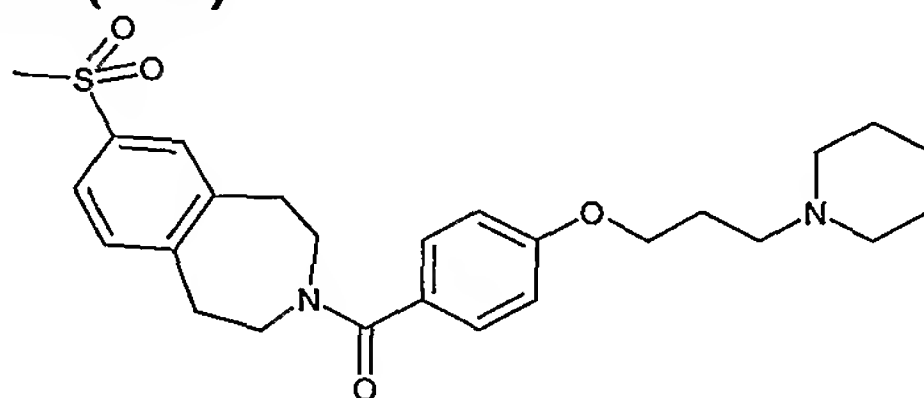
N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (E19)



The title compound was prepared from 4-(3-piperidin-1-ylpropoxy) benzoyl chloride hydrochloride (D3) (0.20g) and 2,3,4,5-tetrahydro-1H-3-benzazepine (WO00/21951) (0.89g) using the procedure described for Example 1 and isolated as a white solid (0.16g). MS electrospray (+ion) 393 (MH⁺). ¹H NMR δ (DMSO-d₆): 9.68 (1H, s), 7.34 (2H, d, J=6.8Hz), 7.14 (4H, m), 7.00 (2H, d, J=6.8Hz), 4.10 (2H, t, J=5.9Hz), 3.81-3.45 (6H, m), 3.17 (2H, m), 2.90 (6H, m), 2.17 (2H, m), 1.83-1.37 (6H, m).

Example 20

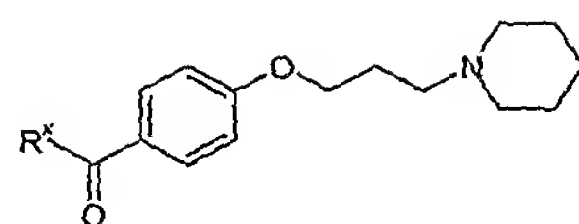
N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (E20)



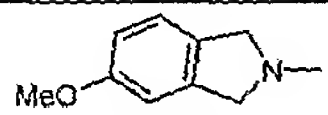
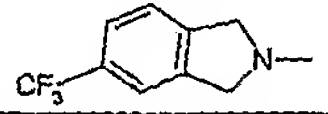
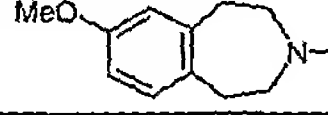
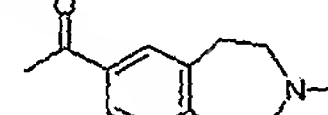
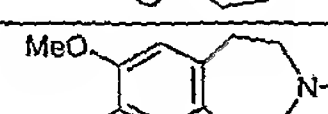
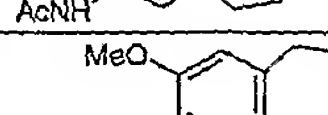
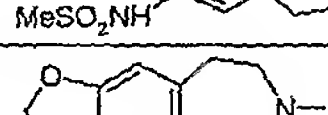
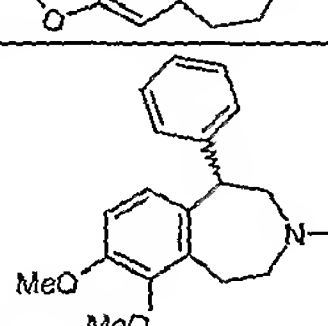
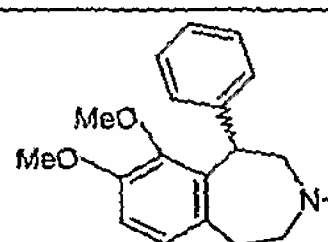
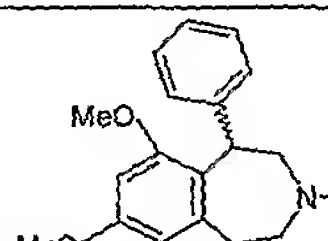
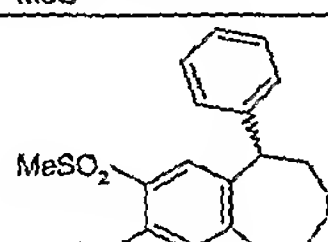
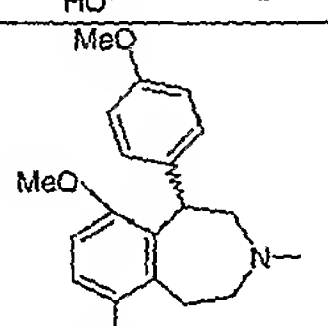
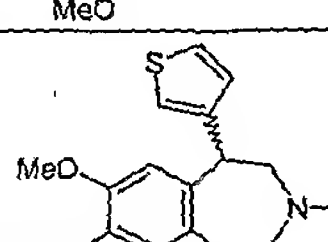
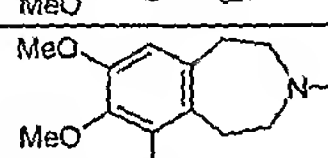
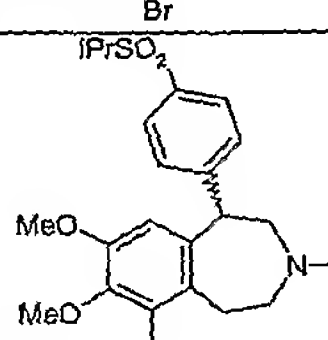
The title compound was prepared from 4-(3-piperidin-1-ylpropoxy) benzoyl chloride hydrochloride (D3) (0.20g) and 7-methanesulfonyl-2,3,4,5-tetrahydro-1H-3-benzazepine (WO00/21951) (0.17g) using the procedure described for Example 1 and isolated as a white solid (0.24g). MS electrospray (+ion) 471 (MH⁺). ¹H NMR δ (DMSO-d₆): 9.83 (1H, s), 7.71 (2H, m), 7.44 (1H, s), 7.35 (2H, d, J=8.5Hz), 7.01 (2H, d, J=8.6Hz), 4.11 (2H, t, J=5.9Hz), 3.71-3.45 (6H, m), 3.18 (6H, m), 3.05 (3H, s), 2.87 (2H, m), 2.20 (2H, m), 1.83-1.37 (6H, m).

Examples 21-49 (E21-E49)

Examples 21 – 49 were prepared from 4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3) and the appropriate amine using the method outlined in Example 11 (E11) and displayed ¹H NMR and mass spectral data that were consistent with structure.

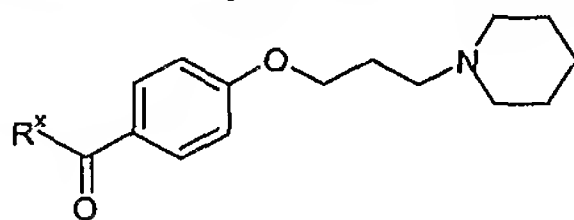


Example No	R ^x	Mass Spectrum (ES ⁺)
E21		[M+H] ⁺ 393
E22		[M+H] ⁺ 463
E23		[M+H] ⁺ 472
E24		[M+H] ⁺ 427
E25		[M+H] ⁺ 443
E26		[M+H] ⁺ 407
E27		[M+H] ⁺ 393
E28		[M+H] ⁺ 393
E29		[M+H] ⁺ 469
E30		[M+H] ⁺ 515
E31		[M+H] ⁺ 439
E32		[M+H] ⁺ 534
E33		[M+H] ⁺ 534
E34		[M+H] ⁺ 455

E35		$[M+H]^+$ 395
E36		$[M+H]^+$ 433
E37		$[M+H]^+$ 424
E38		$[M+H]^+$ 434
E39		$[M+H]^+$ 480
E40		$[M+H]^+$ 516
E41		$[M+H]^+$ 437
E42		$[M+H]^+$ 530
E43		$[M+H]^+$ 530
E44		$[M+H]^+$ 530
E45		$[M+H]^+$ 564
E46		$[M+H]^+$ 559
E47		$[M+H]^+$ 536
E48		$[M+H]^+$ 532
E49		$[M+H]^+$ 669

Examples 50-53 (E50-53)

Examples 50-53 were prepared from 4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3) and the appropriate amine using the method outlined in Example 11 (E11) and displayed ^1H NMR and mass spectral data that were consistent with structure.

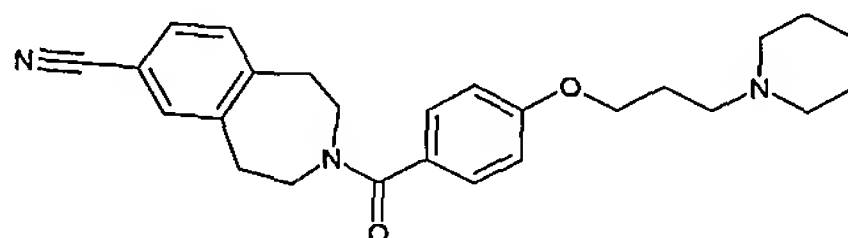


5

Example No	R ^x	Mass Spectrum (ES ⁺)
E50		[M+H] ⁺ 397
E51		[M+H] ⁺ 413, 415
E52		[M+H] ⁺ 447, 449, 451
E53		[M+H] ⁺ 413, 415

Example 54

N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-7-cyano-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (E54)



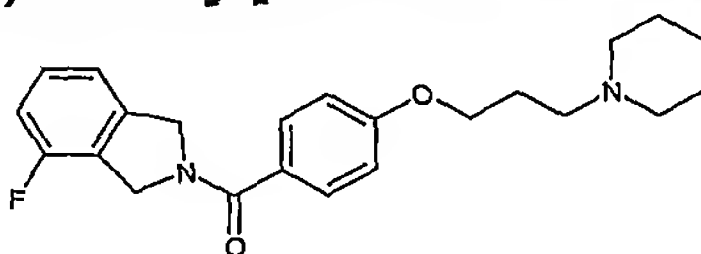
10

A stirred suspension of 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (150mg) in DCM (5ml) at rt was treated with oxalyl chloride (0.1ml) and 10% DMF in DCM (1 drop). After 1h the solution was evaporated and then re-evaporated from DCM (2x5ml). The acid chloride was redissolved in DCM (10ml) and treated with 7-cyano-2,3,4,5-tetrahydro-1H-3-benzazepine (104mg) and diethylaminomethyl polystyrene (3.2mmol/g, 626mg). After stirring overnight the mixture was loaded directly on to a silica gel flash column [step gradient 4-10% MeOH (containing 10% .880 ammonia solution) in DCM]. The required fractions were evaporated, then redissolved in DCM and treated with excess 4M HCl in dioxan. The title compound (E54) (137mg) was obtained by crystallisation from acetone (137mg). MS electrospray (+ion) 418 (MH⁺). ^1H NMR δ (DMSO-d₆): 10.34 (1H, m), 7.65 (2H, m), 7.35 (3H, m), 6.99 (2H, d, J=8.8Hz), 4.11 (2H, t, J=6Hz), 2.70-3.85 (14H, m), 2.19 (2H, m), 1.79 (5H, m), 1.41 (1H, m).

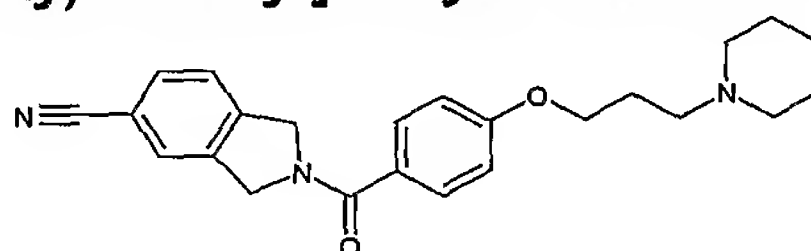
15

20

Example 55

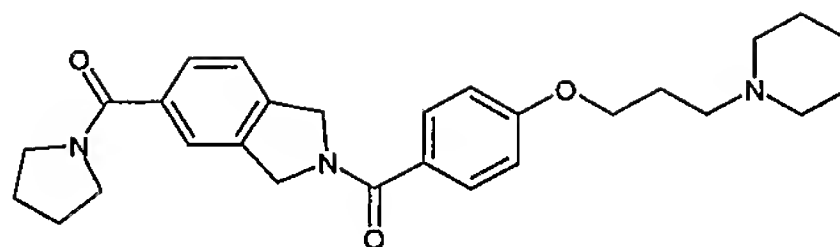
N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-fluoroisoindoline hydrochloride (E55)

A mixture of pentachlorophenyl 4-(3-piperidin-1-ylpropoxy)benzoate (D10) (500mg) and N-benzyl-4-fluoroisoindoline (D9) (200mg) in IPA (10ml) at rt was treated with
 5 poly(methylhydrosiloxane) (0.16ml) and palladium hydroxide on carbon (30mg, 20% Pd) and stirred overnight. The mixture was filtered and evaporated. The residue was redissolved in EtOAc (20ml), washed with saturated sodium hydrogen carbonate solution (10ml), water (2x10ml), brine (10ml), dried (MgSO₄) and evaporated. The residue was chromatographed on a silica gel flash column [step gradient 2-8% MeOH (containing
 10 10% .880 ammonia solution) in DCM]. The required fractions were evaporated, then redissolved in DCM and treated with excess 4M HCl in dioxan. The title compound (E55) (65mg) was obtained by crystallisation from acetone. MS electrospray (+ion) 383 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.15 (1H, m), 7.09-7.65 (7H, m), 4.89 (4H, m), 4.13 (2H, t, J=6Hz), 3.46 (2H, m), 3.16 (2H, m), 2.90 (2H, m), 2.22 (2H, m), 1.79 (5H, m), 1.42 (1H, m).
 15 m).

Example 56**N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-5-cyanoisoindoline hydrochloride (E56)**

A stirred suspension of 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (150mg) in DCM (5ml) at rt was treated with oxalyl chloride (0.1ml) and 10% DMF in DCM (1 drop). After 1h the solution was evaporated and then re-evaporated from DCM (2x5ml). The acid chloride was redissolved in DCM (10ml) and treated with 5-cyanoisoindoline trifluoroacetate (D16) (140mg) and triethylamine (0.3ml) then stirred
 25 overnight and evaporated. The residue was redissolved in EtOAc (20ml), washed with saturated sodium hydrogen carbonate solution (10ml), water (2x10ml), brine (10ml), dried (MgSO₄) and evaporated. The residue was chromatographed on a silica gel flash column [step gradient 2-8% MeOH (containing 10% .880 ammonia solution) in DCM]. The required fractions were evaporated, then redissolved in DCM and treated with
 30 excess 4M HCl in dioxan. The title compound (E56) (60mg) was obtained by crystallisation from acetone. MS electrospray (+ion) 390 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.22 (1H, m), 7.48-7.90 (5H, m), 7.02 (2H, d, J=8.8Hz), 4.89 (4H, m), 4.13 (2H, t, J=6Hz), 3.45 (2H, m), 3.17 (2H, m), 2.88 (2H, m), 2.22 (2H, m), 1.79 (5H, m), 1.40 (1H, m).
 35 m).

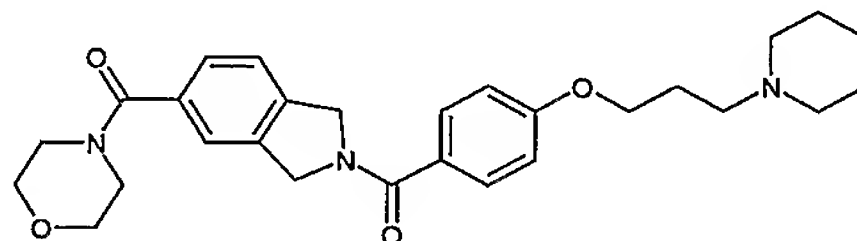
Example 57**N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-5-[(pyrrolidin-1-yl)carbonyl]isoindoline hydrochloride (E57)**



A stirred suspension of 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (101mg) in DCM (5ml) at rt was treated with oxalyl chloride (0.06ml) and 10% DMF in DCM (1 drop). After 1h the solution was evaporated and then re-evaporated from DCM (2x5ml). The acid chloride was redissolved in DCM (10ml) and treated with 5-
 5 [(pyrrolidin-1-yl)carbonyl]isoindoline hydrochloride (D18) (85mg) and diethylaminomethyl polystyrene (3.2mmol/g, 421mg). After stirring overnight the mixture was loaded directly on to a silica gel flash column [step gradient 6-9% MeOH (containing 10% .880 ammonia solution) in DCM]. The required fractions were evaporated, then redissolved in
 10 DCM and treated with excess 4M HCl in dioxan. The title compound (E57) (137mg) was obtained by crystallisation from acetone. MS electrospray (+ion) 390 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.09 (1H, m), 7.00-7.64 (7H, m), 4.86 (4H, m), 4.13 (2H, t, J=6Hz), 3.37 (4H, m), 3.17 (2H, m), 2.89 (2H, m), 2.22 (2H, m), 1.82 (11H, m), 1.41 (1H, m).

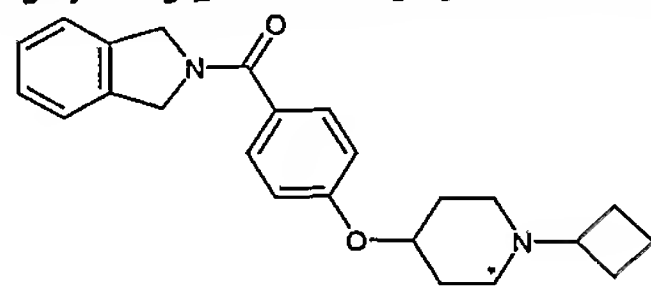
15 Example 58

N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-5-[(morpholin-4-yl)carbonyl]isoindoline hydrochloride (E58)

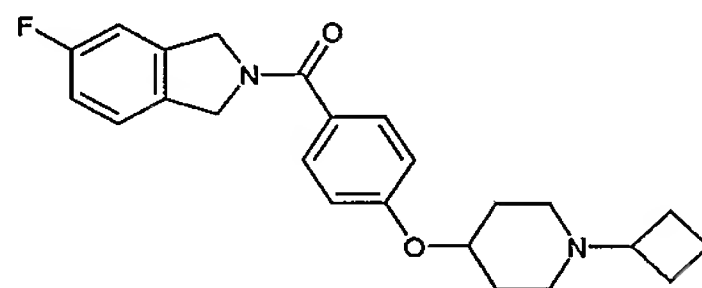


A stirred suspension of 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (262mg) in DCM (5ml) at rt was treated with oxalyl chloride (0.15ml) and 10% DMF in DCM (1 drop). After 1h the solution was evaporated and then re-evaporated from DCM (2x5ml). The acid chloride was redissolved in DCM (10ml) and treated with 5-
 20 [(morpholin-4-yl)carbonyl]isoindoline trifluoroacetate (D20) (305mg) and triethylamine (0.61ml) stirred overnight and evaporated. The residue was redissolved in EtOAc (20ml), washed with saturated sodium hydrogen carbonate solution (10ml), water (2x10ml), brine (10ml), dried (MgSO₄) and evaporated. The residue was
 25 chromatographed on a silica gel flash column [step gradient 6-9% MeOH (containing 10% .880 ammonia solution) in DCM]. The required fractions were evaporated, then redissolved in DCM and treated with excess 4M HCl in dioxan. The title compound
 30 (E58) (170mg) was obtained by crystallisation from EtOH / diethyl ether. MS electrospray (+ion) 478 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.32 (1H, m), 7.62 (2H, d J=8.8Hz), 7.33-7.49 (5H, m), 7.02 (2H, d, J=8.8Hz), 4.86 (4H, m), 4.13 (2H, t, J=6Hz), 3.45 (8H, m), 3.17 (2H, m), 2.92 (2H, m), 2.22 (2H, m), 1.80 (5H, m), 1.41 (1H, m).

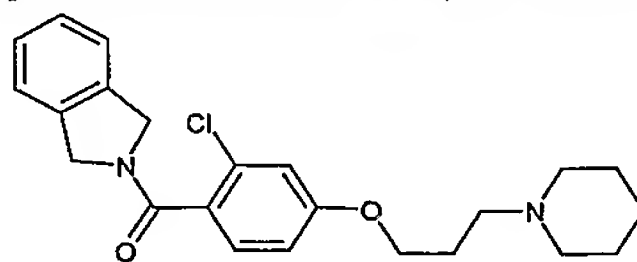
35 Example 59

N-{4-[(1-Cyclobutyl-4-piperidinyloxy]benzoyl}isoindoline hydrochloride (E59)

5 A stirred mixture of 4-[(1-cyclobutyl-4-piperidinyloxy]benzoyl chloride hydrochloride (D25) (0.25g) and diethylaminomethyl polystyrene (3.2 mmol/g, 1.13 g) in DCM (10ml) at rt was treated with isoindoline (0.098g) and stirred for 16h. The reaction mixture was chromatographed directly [silica gel, step gradient 0-10% MeOH (containing 10% .880 ammonia solution) in DCM)]. Fractions containing the required product were evaporated, redissolved in DCM, treated with excess hydrogen chloride (1M solution in diethyl ether) and then concentrated. The residue was crystallised from acetone to yield the title
 10 compound (E59) as a white powder (220mg). MS electrospray (+ion) 377 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.62 (1H, s), 7.62 (2H, m), 7.40-7.25 (4H, m), 7.08 (2H, m), 4.82 (4H, m), 4.64 (1H, m), 3.81-3.58.(1H, m), 3.45-3.20 (2H, m), 2.95 (2H, m), 2.38-1.62 (10H, m).

Example 60**N-{4-[(1-Cyclobutyl-4-piperidinyloxy]benzoyl}-5-fluoro-isoindoline hydrochloride (E60)**

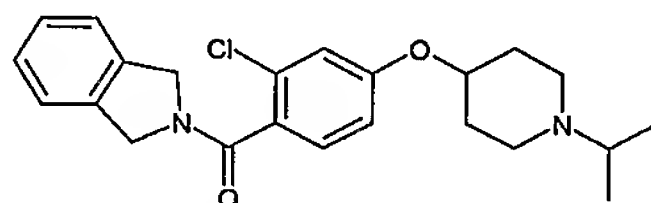
20 A stirred mixture of 4-[(1-cyclobutyl-4-piperidinyloxy]benzoyl chloride hydrochloride (D25) (0.20 g) and diethylaminomethyl polystyrene (3.2 mmol/g, 0.80g) in DCM (10ml) at rt was treated with 5-fluoroisoindoline (0.101 g) and stirred for 16h. The reaction mixture was chromatographed directly [silica gel, step gradient 0-10% MeOH (containing 10% .880 ammonia solution) in DCM)]. Fractions containing the required product were evaporated, redissolved in DCM, treated with excess hydrogen chloride (1M solution in
 25 diethyl ether) and then concentrated. The residue was crystallised from acetone to yield the title compound (E60) as a white powder (150mg). MS electrospray (+ion) 395 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.60 (1H, s), 7.62 (2H, m), 7.42-7.06 (5H, m), 4.85 (4H, m), 4.66 (1H, m), 3.75-3.55 (1H, m), 3.45-3.20 (2H, m), 2.90 (2H, m), 2.41-1.62 (10H, m).

Example 61**N-[2-Chloro-4-(3-Piperidin-1-ylpropoxy)benzoyl]isoindoline hydrochloride (E61)**

A stirred mixture of 2-chloro-4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D28) (0.10g) and diethylaminomethyl polystyrene (3.2 mmol/g, 0.8 g) in DCM (10ml) at rt was treated with isoindoline (0.031g) and stirred for 16h. The reaction mixture was chromatographed directly [silica gel, step gradient 0-10% MeOH (containing 10% .880 ammonia solution) in DCM]. Fractions containing the required product were evaporated, redissolved in DCM, treated with excess hydrogen chloride (1M solution in diethyl ether) and then concentrated. The residue was crystallised from acetone to yield the title compound (E61) as a white solid (0.083g). MS electrospray (+ion) 399/401 (MH⁺). ¹H NMR δ (DMSO-d₆): 9.90 (1H, s), 7.41 (2H, m), 7.28 (3H, m), 7.11 (1H, s), 7.02 (1H, m), 4.83 (2H, s), 4.50 (2H, s), 4.14 (2H, t, J=5.9Hz), 3.45 (2H, m), 3.25 (2H, m), 2.90 (2H, m), 2.18 (2H, m), 1.87-1.30 (6H, m).

Example 62

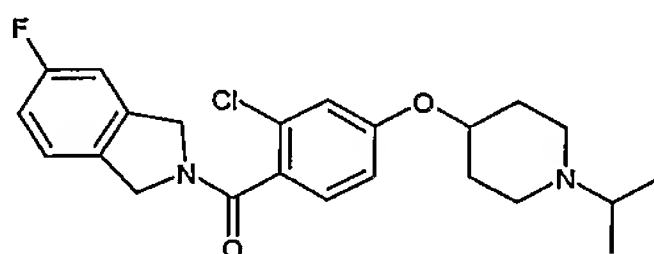
N-{2-Chloro-4-[(1-isopropyl-4-piperidinyloxy]benzoyl}isoindoline hydrochloride (E62)



A stirred mixture of 2-chloro-4-[(1-isopropyl-4-piperidinyloxy]benzoyl chloride hydrochloride (D33) (0.20 g) and diethylaminomethyl polystyrene (3.2 mmol/g, 1.0 g) in DCM (10ml) at rt was treated with isoindoline (0.08 g) and stirred for 16h. The reaction mixture was chromatographed directly [silica gel, step gradient 0-10% MeOH (containing 10% .880 ammonia solution) in DCM]. Fractions containing the required product were evaporated, redissolved in DCM, treated with excess hydrogen chloride (1M solution in diethyl ether) and then concentrated. The residue was crystallised from acetone to yield the title compound (E62) as a white solid (0.09g). MS electrospray (+ion) 399/401 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.90 (1H, s), 7.33-7.10 (6H, m), 6.96 (1H, m), 4.82-4.51 (3H, m), 4.39 (3H, m), 3.35 (2H, m), 3.00 (2H, m), 2.11-1.80 (4H, m), 1.17 (6H, m).

Example 63

N-{2-Chloro-4-[(1-isopropyl-4-piperidinyloxy]benzoyl}-5-fluoro-isoindoline hydrochloride (E63)



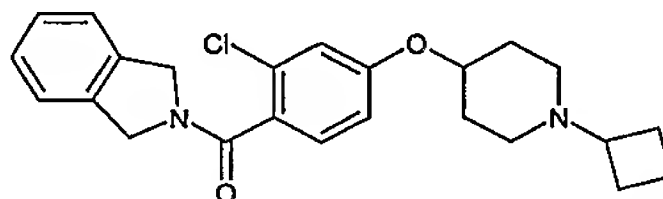
A stirred mixture of 2-chloro-4-[(1-isopropyl-4-piperidinyloxy]benzoyl chloride hydrochloride (D33) (0.20g) and diethylaminomethyl polystyrene (3.2 mmol/g, 1.0g) in DCM (10ml) at rt was treated with 5-fluoroisoindoline hydrochloride (D8) (0.10g) and stirred for 16h. The reaction mixture was chromatographed directly [silica gel, step gradient 0-10% MeOH (containing 10% .880 ammonia solution) in DCM]. Fractions containing the required product were evaporated, redissolved in DCM, treated with excess hydrogen chloride (1M solution in diethyl ether) and then concentrated. The

residue was crystallised from acetone to yield the title compound (E63) as a white solid (0.09g). MS electrospray (+ion) 417/419 (MH⁺). ¹H NMR δ (DMSO-d₆): 9.80 (1H, s), 7.22-6.81 (6H, m), 4.70-4.39 (3H, m), 4.25 (3H, m), 3.24 (2H, m), 2.88 (2H, m), 2.10-1.70 (4H, m), 1.06 (6H, m).

5

Example 64

N-{2-Chloro-4-[(1-cyclobutyl-4-piperidinyloxy]benzoyl}isoindoline hydrochloride (E64)

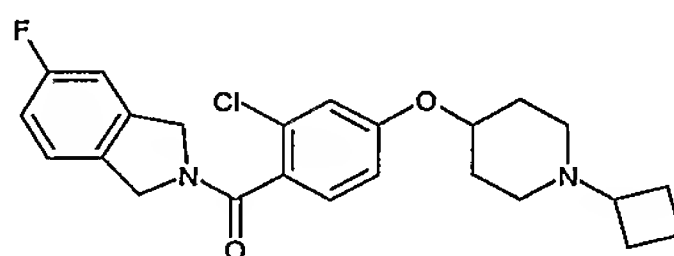


10 A stirred mixture of 2-chloro-4-[(1-cyclobutyl-4-piperidinyloxy]benzoyl chloride hydrochloride (D36) (0.20g) and diethylaminomethyl polystyrene (3.2 mmol/g, 1.0g) in DCM (10ml) at rt was treated with isoindoline (0.08g) and stirred for 16h. The reaction mixture was chromatographed directly [silica gel, step gradient 0-10% MeOH (containing 10% .880 ammonia solution) in DCM]. Fractions containing the required product were
15 evaporated, redissolved in DCM, treated with excess hydrogen chloride (1M solution in diethyl ether) and then concentrated. The residue was crystallised from acetone to yield the title compound as a white solid (0.08g). MS electrospray (+ion) 411/413 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.55 (1H, s), 7.45 (2H, m), 7.27 (4H, m), 7.11 (1H, m), 4.89-4.68 (3H, m), 4.52 (2H, m), 3.67 (1H, m), 3.46-3.18 (2H, m), 2.90 (2H, m), 2.40-1.63 (10H, m).

20

Example 65

N-{2-Chloro-4-[(1-cyclobutyl-4-piperidinyloxy]benzoyl}-5-fluoro-isoindoline hydrochloride (E65)



25 A stirred mixture of 2-chloro-4-[(1-cyclobutyl-4-piperidinyloxy]benzoyl chloride hydrochloride (D36) (0.20g) and diethylaminomethyl polystyrene (3.2 mmol/g, 0.8g) in DCM (10ml) at rt was treated with 5-fluoroisoindoline hydrochloride (D8) (0.10g) and stirred for 16h. The reaction mixture was chromatographed directly [silica gel, step gradient 0-10% MeOH (containing 10% .880 ammonia solution) in DCM]. Fractions
30 containing the required product were evaporated, redissolved in DCM, treated with excess hydrogen chloride (1M solution in diethyl ether) and then concentrated. The residue was crystallised from acetone to yield the title compound (E65) as a white solid (0.14g). MS electrospray (+ion) 430/432 (MH⁺). ¹H NMR δ (DMSO-d₆): 10.48 (1H, s), 7.46-7.06 (6H, m), 4.88-4.60 (3H, m), 4.51 (2H, m), 3.80-3.55 (1H, m), 3.46-3.18 (2H, m), 2.88 (2H, m), 2.38-1.64 (10H, m).

35

Preparation of precursors

Certain precursors referred to in the preparation of the above Examples were prepared from the following references:

Substituted isoindolines: 5-Fluoroisoindoline (W. Adcock et al., Aust J Chem 1976, 29, 2571), 5-methoxyisoindoline and 5-trifluoromethoxyisoindoline (N E Austin et al., Bioorg Med Chem Lett., 2001, 11, 5, 685), 5-nitroisoindoline (Fraenkel, Chem Ber 1900, 33, 2811).

Substituted 1,2,3,4-tetrahydroisoquinolines: 6-cyano-1,2,3,4-tetrahydroisoquinoline (WO9850363, SmithKline Beecham), 7-cyano-1,2,3,4-tetrahydroisoquinoline (WO9850364, SmithKline Beecham). Preparation of additional substituted 1,2,3,4-tetrahydroisoquinolines : G E Stocker, Tet. Lett., 1996, 37 (31), 5453.

Substituted benzazepines: 7-cyano-2,3,4,5-tetrahydro-1*H*-3-benzazepine, 7-acetyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine and 7-methylsulfonyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (WO0021951, SmithKline Beecham, N E Austin et al., Bioorg Med Chem Lett., 2000, 10, 22, 2553). 1-Aryl-2,3,4,5-tetrahydro-1*H*-3-benzazepines (J. Med Chem., 1986, 29 (11), 2315).

Abbreviations

Boc	tert-butoxycarbonyl
EtOAc	ethyl acetate
h	hour
min	minutes
DCM	dichloromethane
MeOH	methanol
rt	room temperature
DCC	dicyclohexylcarbodiimide
DMF	dimethylformamide
IPA	isopropanol
TFA	trifluoroacetic acid
HOBT	1-hydroxybenzotriazole
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Biological Data

A membrane preparation containing histamine H3 receptors may be prepared in accordance with the following procedures:

(i) Generation of histamine H3 cell line

DNA encoding the human histamine H3 gene (Huvar, A. *et al.* (1999) Mol. Pharmacol. **55(6)**, 1101-1107) was cloned into a holding vector, pCDNA3.1 TOPO (InVitrogen) and its cDNA was isolated from this vector by restriction digestion of plasmid DNA with the enzymes BamH1 and Not-1 and ligated into the inducible expression vector pGene (InVitrogen) digested with the same enzymes. The GeneSwitch™ system (a system where in transgene expression is switched off in the absence of an inducer and switched on in the presence of an inducer) was performed as described in US Patent nos:

5,364,791; 5,874,534; and 5,935,934. Ligated DNA was transformed into competent DH5α E. coli host bacterial cells and plated onto Luria Broth (LB) agar containing Zeocin™ (an antibiotic which allows the selection of cells expressing the sh ble gene which is present on pGene and pSwitch) at 50µg ml⁻¹. Colonies containing the re-ligated plasmid were identified by restriction analysis. DNA for transfection into mammalian cells was prepared from 250ml cultures of the host bacterium containing the pGeneH3 plasmid and isolated using a DNA preparation kit (Qiagen Midi-Prep) as per manufacturers guidelines (Qiagen).

CHO K1 cells previously transfected with the pSwitch regulatory plasmid (InVitrogen) were seeded at 2x10⁶ cells per T75 flask in Complete Medium, containing Hams F12 (GIBCOBRL, Life Technologies) medium supplemented with 10% v/v dialysed foetal bovine serum, L-glutamine, and hygromycin (100µg ml⁻¹), 24 hours prior to use. Plasmid DNA was transfected into the cells using Lipofectamine plus according to the manufacturers guidelines (InVitrogen). 48 hours post transfection cells were placed into complete medium supplemented with 500µg ml⁻¹ Zeocin™.

10-14 days post selection 10nM Mifepristone (InVitrogen), was added to the culture medium to induce the expression of the receptor. 18 hours post induction cells were detached from the flask using ethylenediamine tetra-acetic acid (EDTA; 1:5000; InVitrogen), following several washes with phosphate buffered saline pH 7.4 and resuspended in Sorting Medium containing Minimum Essential Medium (MEM), without phenol red, and supplemented with Earles salts and 3% Foetal Clone II (Hyclone).

Approximately 1x 10⁷ cells were examined for receptor expression by staining with a rabbit polyclonal antibody, 4a, raised against the N-terminal domain of the histamine H3 receptor, incubated on ice for 60 minutes, followed by two washes in sorting medium. Receptor bound antibody was detected by incubation of the cells for 60 minutes on ice with a goat anti rabbit antibody, conjugated with Alexa 488 fluorescence marker (Molecular Probes). Following two further washes with Sorting Medium, cells were filtered through a 50µm Filcon™ (BD Biosciences) and then analysed on a FACS Vantage SE Flow Cytometer fitted with an Automatic Cell Deposition Unit. Control cells were non-induced cells treated in a similar manner. Positively stained cells were sorted as single cells into 96-well plates, containing Complete Medium containing 500µg ml⁻¹ Zeocin™ and allowed to expand before reanalysis for receptor expression via antibody and ligand binding studies. One clone, 3H3, was selected for membrane preparation.

(ii) Membrane preparation from cultured cells

All steps of the protocol are carried out at 4°C and with pre-cooled reagents. The cell pellet is resuspended in 10 volumes of buffer A2 containing 50mM N-2-

- 5 hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) (pH 7.40) supplemented with 10e-4M leupeptin (acetyl-leucyl-leucyl-arginal; Sigma L2884), 25µg/ml bacitracin (Sigma B0125), 1mM ethylenediamine tetra-acetic acid (EDTA), 1mM phenylmethylsulfonyl fluoride (PMSF) and 2x10e-6M pepstain A (Sigma). The cells are then homogenised by 2 x 15 second bursts in a 1 litre glass Waring blender, followed by centrifugation at 500g
10 for 20 minutes. The supernatant is then spun at 48,000g for 30 minutes. The pellet is resuspended in 4 volumes of buffer A2 by vortexing for 5 seconds, followed by homogenisation in a Dounce homogeniser (10-15 strokes). At this point the preparation is aliquoted into polypropylene tubes and stored at -70°C.

- 15 Compounds of the invention may be tested for in vitro biological activity in accordance with the following assays:

(I) Histamine H3 binding assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is
20 added:-

- (a) 10µl of test compound (or 10µl of iodophenpropit (a known histamine H3 antagonist) at a final concentration of 10mM) diluted to the required concentration in 10% DMSO;
(b) 10µl ¹²⁵I 4-[3-(4-iodophenylmethoxy)propyl]-1H-imidazolium (iodoproxyfan)
25 (Amersham; 1.85MBq/µl or 50µCi/ml; Specific Activity ~2000Ci/mmol) diluted to 200pM in assay buffer (50mM Tris(hydroxymethyl)aminomethane buffer (TRIS) pH 7.4, 0.5mM ethylenediamine tetra-acetic acid (EDTA)) to give 20pM final concentration; and
(c) 80µl bead/membrane mix prepared by suspending Scintillation Proximity Assay (SPA) bead type WGA-PVT at 100mg/ml in assay buffer followed by mixing with
30 membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 80µl which contains 7.5µg protein and 0.25mg bead per well – mixture was pre-mixed at room temperature for 60 minutes on a roller. The plate is shaken for 5 minutes and then allowed to stand at room temperature for 3-4
35 hours prior to reading in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data was analysed using a 4-parameter logistic equation.

(II) Histamine H3 functional antagonist assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is
added:-

- 40 (a) 10µl of test compound (or 10µl of guanosine 5'- triphosphate (GTP) (Sigma) as non-specific binding control) diluted to required concentration in assay buffer (20mM N-

2-Hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) + 100mM NaCl + 10mM MgCl₂, pH7.4 NaOH);

- (b) 60μl bead/membrane/GDP mix prepared by suspending wheat germ agglutinin-polyvinyltoluene (WGA-PVT) scintillation proximity assay (SPA) beads at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 60μl which contains 10μg protein and 0.5mg bead per well – mixture is pre-mixed at 4°C for 30 minutes on a roller and just prior to addition to the plate, 10μM final concentration of guanosine 5' diphosphate (GDP) (Sigma; diluted in assay buffer) is added;
- 10 The plate is incubated at room temperature to equilibrate antagonist with receptor/beads by shaking for 30 minutes followed by addition of:
- (c) 10μl histamine (Tocris) at a final concentration of 0.3μM; and
- (d) 20μl guanosine 5' [γ35-S] thiotriphosphate, triethylamine salt (Amersham; radioactivity concentration = 37kBq/μl or 1mCi/ml; Specific Activity 1160Ci/mmol) diluted to 1.9nM in assay buffer to give 0.38nM final.
- 15 The plate is then incubated on a shaker at room temperature for 30 minutes followed by centrifugation for 5 minutes at 1500 rpm. The plate is read between 3 and 6 hours after completion of centrifuge run in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data is analysed using a 4-parameter logistic equation. Basal activity used as minimum i.e. histamine not added to well.
- 20

Results

- The compounds of Examples E1-E49 were tested in the histamine H3 functional antagonist assay and exhibited pK_b values ≥ 7.5. In particular, Examples E1-2, E4-12, E15-19, E21-31, E33, E35-36, E38-39, E41-42, E44-45, E47, E50-51, E54-55, E59-61 and E64-65 exhibited pK_b values ≥ 8.5.
- 25

R¹¹ and R¹² independently represent C₁₋₆ alkyl or together with the nitrogen atom to which they are attached represent an N-linked heterocyclic group optionally substituted by one or two R¹⁷ groups;

R¹³ represents hydrogen, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, -C₁₋₆ alkyl-aryl or heterocyclyl;

5 R¹⁴ and R¹⁷ independently represent halogen, C₁₋₆ alkyl, haloC₁₋₆ alkyl, OH, diC₁₋₆ alkylamino or C₁₋₆ alkoxy;

f and k independently represent 0, 1 or 2;

g is 0, 1 or 2 and h is 0, 1, 2 or 3, such that g and h cannot both be 0;
or solvates thereof.

10

2. A compound as defined in claim 1 wherein R¹ represents halogen, hydroxy, cyano, nitro, -NR¹⁵R¹⁶, -NR¹⁵COR¹⁶, polyhaloC₁₋₆ alkyl, heterocyclyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylsulfonyl, C₁₋₆ alkylsulfinyl, C₁₋₆ alkanoyl, arylsulfonamido, arylaminosulfonyl, -NR¹⁵SO₂R¹⁶, -SO₂NR¹⁵R¹⁶, -CO-heterocyclyl or two R¹ groups are
15 linked to form a heterocyclyl group.

3. A compound as defined in claim 2 wherein p represents 1 and R¹ represents fluoro or cyano.

20

4. A compound as defined in claim 1 wherein p represents 0.

5. A compound as defined in any one of claims 1 to 4 wherein m represents 1 and R² represents C₁₋₆ alkyl, arylC₁₋₆ alkyl, aryl or heteroaryl.

25

6. A compound as defined in any one of claims 1 to 4 wherein m represents 0.


7. A compound as defined in any one of claims 1 to 6 wherein n represents 1 and R³ represents halogen or polyhaloC₁₋₆ alkyl.

30

8. A compound as defined in any one of claims 1 to 6 wherein n represents 0.

9. A compound as defined in any one of claims 1 to 8 wherein a is 1 and b is 0.

35

10. A compound as defined in any one of claims 1 to 9 wherein  is a single bond.

11. A compound as defined in any one of claims 1 to 10 wherein -O-R⁴ is present on the phenyl group at the 4-position.

40

12. A compound as defined in any one of claims 1 to 11 wherein R⁴ represents - (CH₂)_q-NR¹¹R¹², q represents 3 and NR¹¹R¹² represents unsubstituted piperidine.

13. A compound as defined in any one of claims 1 to 11 wherein R⁴ represents a group of formula (i), f represents 0, h represents 1, g represents 2, k represents 0 and R¹³ represents C₃₋₈ cycloalkyl.

- 5 14. A compound according to claim 1 which is
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]indoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-3,4-dihydro-1H-isoquinoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-5-bromoindoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]indole;
 10 5-Fluoro-2-methyl-N-[4-(3-piperidin-1-ylpropoxy)benzoyl]-indole;
 5-Methoxy-2-methyl-N-[4-(3-piperidin-1-ylpropoxy)benzoyl]-indole;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-5-fluoroindoline;
 (±)-N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-2-methylindoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-1,2,3,4-tetrahydroquinoline;
 15 N-[4-(3-Piperidin-1-ylpropoxy)-benzoyl]-5-nitroisoindoline;
 N-[4-(3-Piperidin-1-ylpropoxy)-benzoyl]-5-aminoisoindoline;
 N-[4-(3-Piperidin-1-ylpropoxy)-benzoyl]-5-(1-succinimido)-isoindoline;
 N-[4-(3-Piperidin-1-ylpropoxy)-benzoyl]-5-(2-oxo-pyrrolidin-1-yl)-isoindoline;
 N-[4-(3-Piperidin-1-ylpropoxy)-2-trifluoromethyl-benzoyl]isoindoline;
 20 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-6-cyano-1,2,3,4-tetrahydroisoquinoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-7-cyano-1,2,3,4-tetrahydroisoquinoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-2,3,4,5-tetrahydro-1H-3-benzazepine;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-7-methylsulfonyl-2,3,4,5-tetrahydro-1H-3-
 benzazepine;
 25 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-3,3-dimethylindoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-5-methoxy-6-trifluoromethyl-indoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-5-(dimethylaminosulfonyl)-indoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-5-(methylsulfinyl)-indoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-5-(methylsulfonyl)-indoline;
 30 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-5-acetyl-indoline;
 (±)-N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-6-methyl-1,2,3,4-tetrahydroquinoline;
 (±)-N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-1-benzyl-1,2,3,4-tetrahydroisoquinoline;
 (±)-N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-1-phenyl-6,7-dimethoxy-1,2,3,4-
 35 tetrahydroisoquinoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-5-(phenylsulfonamido)-1,2,3,4-
 tetrahydroisoquinoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-7-(phenylaminosulfonyl)-1,2,3,4-
 40 tetrahydroisoquinoline;
 (±)-N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-1-phenyl-1,2,3,4-tetrahydroisoquinoline;
 N-[4-(3-Piperidin-1-ylpropoxy)-benzoyl]-5-methoxyisoindoline;

- N-[4-(3-Piperidin-1-ylpropoxy)-benzoyl]-5-trifluoromethylisoindoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-7-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-7-acetyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-7-acetylamino-8-methoxy-2,3,4,5-tetrahydro-1*H*-
 5 3-benzazepine;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-7-methylsulfonamido-8-methoxy-2,3,4,5-
 tetrahydro-1*H*-3-benzazepine;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-6,7,8,9-tetrahydro-5*H*-[1,3]dioxolo[4,5-
h][3]benzazepine;
 10 (±)-N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-1-phenyl-6,7-dimethoxy-2,3,4,5-tetrahydro-
 1*H*-3-benzazepine;
 (±)-N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-1-phenyl-8,9-dimethoxy-2,3,4,5-tetrahydro-
 1*H*-3-benzazepine;
 (±)-N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-1-phenyl-7,9-dimethoxy-2,3,4,5-tetrahydro-
 15 1*H*-3-benzazepine;
 (±)-N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-1-phenyl-7-hydroxy-8-methylsulfonyl-2,3,4,5-
 tetrahydro-1*H*-3-benzazepine;
 (±)-N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-1-(4-methoxyphenyl)-6,9-dimethoxy-2,3,4,5-
 tetrahydro-1*H*-3-benzazepine;
 20 (±)-N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-1-thienyl-7,8-dimethoxy-2,3,4,5-tetrahydro-
 1*H*-3-benzazepine;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-6-bromo-7,8-dimethoxy-2,3,4,5-tetrahydro-1*H*-3-
 benzazepine;
 (±)-N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-1-(4-*i*-propylsulfonyl)-6-chloro-7,8-
 25 dimethoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-7-fluoro-1,2,3,4-tetrahydroisoquinoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-6-chloro-1,2,3,4-tetrahydroisoquinoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-7,8-dichloro-1,2,3,4-tetrahydroisoquinoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-8-chloro-1,2,3,4-tetrahydroisoquinoline;
 30 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-7-cyano-2,3,4,5-tetrahydro-1*H*-3-benzazepine; N-
 [4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-fluoroisoindoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-5-cyanoisoindoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-5-[(pyrrolidin-1-yl)carbonyl]isoindoline;
 N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-5-[(morpholin-4-yl)carbonyl]isoindoline;
 35 N-[2-Chloro-4-(3-Piperidin-1-ylpropoxy)benzoyl]isoindoline;
 N-{2-Chloro-4-[(1-isopropyl-4-piperidinyl)oxy]benzoyl}isoindoline;
 N-{2-Chloro-4-[(1-isopropyl-4-piperidinyl)oxy]benzoyl}-5-fluoro-isoindoline;
 N-{2-Chloro-4-[(1-cyclobutyl-4-piperidinyl)oxy]benzoyl}isoindoline; or
 N-{2-Chloro-4-[(1-cyclobutyl-4-piperidinyl)oxy]benzoyl}-5-fluoro-isoindoline
 40 or a pharmaceutically acceptable salt thereof.

15. A compound according to claim 1 which is:

N-[4-(3-Piperidin-1-ylpropoxy)-benzoyl]-5-fluoroisoindoline;
 N-{4-[(1-Cyclobutyl-4-piperidinyl)oxy]benzoyl}isoindoline; or
 N-{4-[(1-Cyclobutyl-4-piperidinyl)oxy]benzoyl}-5-fluoro-isoindoline
 or a pharmaceutically acceptable salt thereof.

5

16. A compound according to claim 1 which is N-[4-(3-piperidin-1-ylpropoxy)benzoyl]isoindoline or a pharmaceutically acceptable salt thereof.

10

17. A pharmaceutical composition which comprises the compound of formula (I) as defined in any one of claims 1 to 16 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

18 A compound as defined in any one of claims 1 to 16 for use in therapy.

15

19. A compound as defined in any one of claims 1 to 16 for use in the treatment of neurological diseases.

20

20. Use of a compound as defined in any one of claims 1 to 16 in the manufacture of a medicament for the treatment of neurological diseases.

21. A method of treatment of neurological diseases which comprises administering to a host in need thereof an effective amount of a compound of formula (I) as defined in any one of claims 1 to 16 or a pharmaceutically acceptable salt thereof.

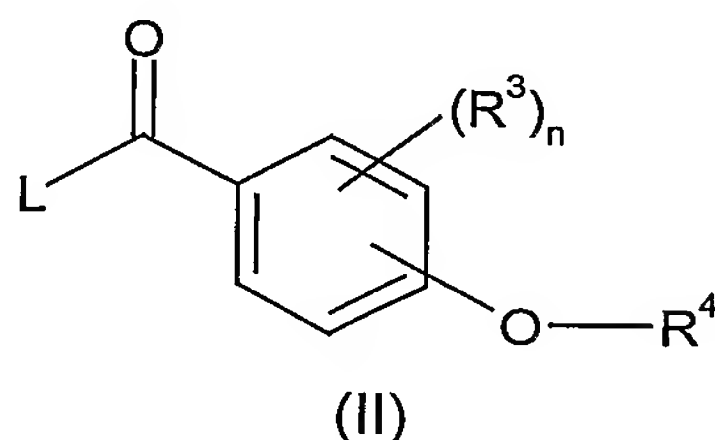
25

22. A pharmaceutical composition for use in the treatment of neurological diseases which comprises the compound of formula (I) as defined in any one of claims 1 to 16 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

30

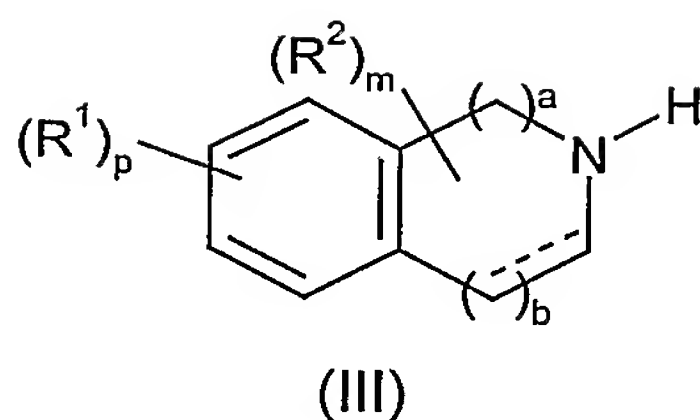
23. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) reacting a compound of formula (II)



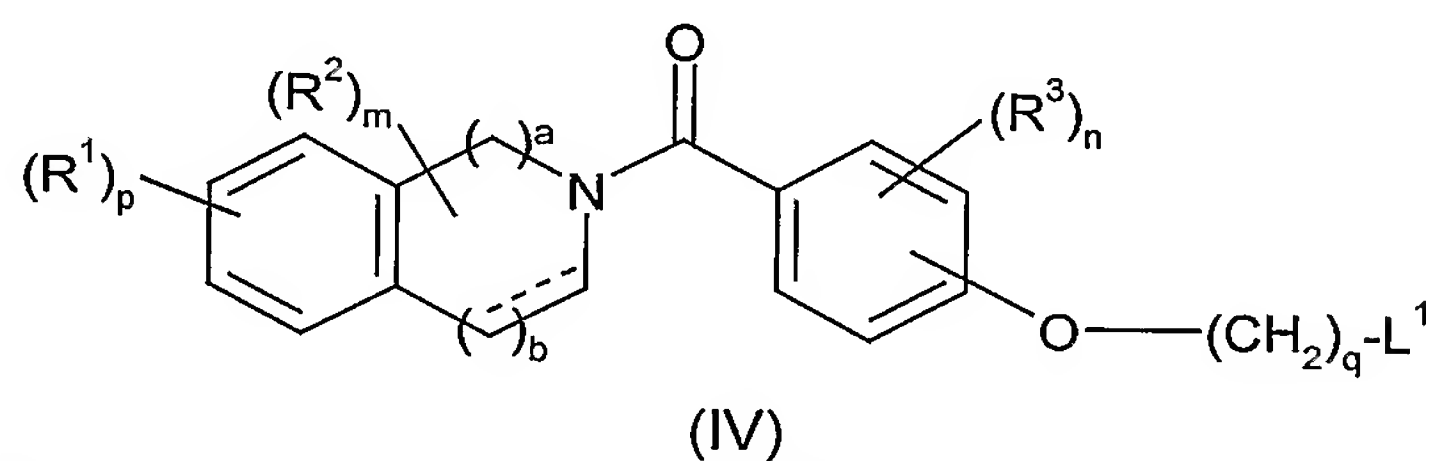
35

with a compound of formula (III)



5 or a protected derivative thereof, wherein R^1 , R^2 , R^3 , R^4 , a , b , m , n and p are as defined in claim 1 and L is OH or a suitable leaving group; or

(b) preparing a compound of formula (I) wherein R^4 represents $-(CH_2)_q-NR^{11}R^{12}$ which comprises reacting a compound of formula (IV)



10 wherein R^1 , R^2 , R^3 , a , b , m , n , p and q are as defined in claim 1 and L^1 represents a suitable leaving group with a compound of formula $HNR^{11}R^{12}$; wherein R^{11} and R^{12} are as defined in claim 1; and optionally thereafter

15 (c) deprotecting a compound of formula (I) which is protected; and optionally thereafter

(d) interconversion to other compounds of formula (I).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/11650

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/26 C07D217/06 C07D209/44 C07D209/32 C07D215/08
C07D403/04 C07D223/16 C07D409/04 C07D491/04 C07D403/12
A61K31/4035 A61K31/404 A61K31/47 A61K31/55 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02 076925 A (ELI LILLY AND COMPANY, USA) 3 October 2002 (2002-10-03) cited in the application claims 1,14-19; examples 41-44,102,103,155,173 ----	1-23
Y	WO 02 24695 A (ORTHO MCNEIL PHARM INC) 28 March 2002 (2002-03-28) claims 1,23-25; examples 16,63-69 ---	1-23
Y	WO 02 12190 A (ORTHO MCNEIL PHARM INC) 14 February 2002 (2002-02-14) cited in the application claims 1,48-51; examples 9,31,54,76 --- -/--	1-23

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

13 January 2004

Date of mailing of the international search report

27/01/2004

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/11650

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 06254 A (SCHUNACK WALTER G ; SIGURD ELZ (DE); STARK HOLGER (DE); BIOPROJET S) 10 February 2000 (2000-02-10) cited in the application claims 79-81; examples 76,90,160 ---	1-23
Y	WO 01 23374 A (WYMAN PAUL ADRIAN ; MARSHALL HOWARD (GB); THOMPSON MERVYN (GB); SMI) 5 April 2001 (2001-04-05) cited in the application page 7, line 17 - line 31; claims 1,12,13 ---	1-23
A	WO 01 066520 A (ONO PHARMACEUTICAL) 13 September 2001 (2001-09-13) cited in the application -& EP 1 262 475 A 4 December 2002 (2002-12-04) examples 7(19) p.114, 7(24) p.117 and 7(54), p.132 page 9, line 35 -page 10, line 45; claim 1 ---	1-18,23
X,P	WO 02 094788 A (ELI LILLY AND COMPANY, USA) 28 November 2002 (2002-11-28) cited in the application examples 1-4 -----	1-18,23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/11650

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 19,21-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/EP 03/11650

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 02076925	A	03-10-2002	CA 2441080 A1	03-10-2002
			WO 02076925 A2	03-10-2002
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